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PRESIDENTIAL ADDRESS*

F. BAYARD CARTER, M.D., DURHAM, N. C.

THE honor of serving as President of the South Atlantic Association of Obstetricians and Gynecologists is truly and sincerely appreciated. To follow in this office J. R. McCord of Georgia, Robert E. Seibels of South Carolina, M. Pierce Rucker of Virginia, R. A. Bartholomew of Georgia, Oren Moore of North Carolina, Robert A. Ross of North Carolina, J. Randolph Perdue of Florida, Tiffany J. Williams of Virginia, S. Royall Norris of Florida, C. J. Andrews of Virginia, Lester A. Wilson of South Carolina, and E. D. Colvin of Georgia engenders a true sense of humility and an awareness of an unspoken obligation.

Any man would hope to bring to the Association more than he ever could possibly bring. He would wish, in his obligatory presidential address, to present something strikingly original and vital. The ability to do this is given to a few men and your present president cannot claim that ability. Were he a superstitious individual he would hesitate to speak, because he finds that, although this is our fifteenth annual meeting, he is in fact the thirteenth Fellow to serve in this office.

The stated purpose of the Association is "to encourage study of the problems of Obstetrics and Gynecology; to improve the quality of Obstetrical

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and Gynecological practice both of its Fellows and of all other physicians residing in its territory," etc. In these words we have stated an obligation.

In this presentation we ask ourselves how in the formulation and the conduct of our scientific programs may we improve the study of the manifold problems which arise in the practice and in the teaching of obstetrics and gynecology?

For your consideration it is suggested that a part of our yearly scientific program be filled by men of outstanding knowledge and attainments in preclinical and clinical fields related to, but not a part of, our specialties. In the field of endocrinology we need critical and constant discipline.

There are teachers of anatomy and embryology who teach modern, dynamic subjects related to our fields. Physiologists, biochemists and pharmacologists have much cogent information for us if we persist in a systematic manner over a period of years in attracting them to our programs.

Bacteriology stands in singular neglect in the practice and the writings of our groups. We must admit our ignorance and ensure for the future certain proper curative procedures applied under the guidance of experts in that branch of science.

Pathology is so important, both to our clinical work and to our patients of the future, that it should have a regular place in our programs. It can be modern, clinical, and dynamic.

In internal medicine we have so wide a selection of subjects that our opportunities are legion. We might in considered and orderly manner utilize the knowledge of the internist, of the cardiologist, of the metabolism expert, of the hematologist, of the phthisiologist, of the allergist, of the dermatologist, of the neurologist, and of the gastroenterologist.

The growing demand for good psychiatry in obstetric and gynecologic practice and teaching is quite evident. Certainly the application of qualified and considered psychiatric practice to many of the obstetric and gynecologic complaints, has led to a marked reduction in ill-advised and misused therapeutic and operative procedures. The combination of a good psychiatrist and a good pathologist with a man well-trained in obstetrics and gynecology gives the best guarantee of conservative and adequate diagnostic and therapeutic measures.

We also need elucidation of the possibilities of occupational and physical therapies in their sensible and practical applications.

Each day we deal with public health problems and we should have the benefit of the approach, of the surveys, and of the methodology used in this field. It would also be beneficial from time to time to have instruction by a good statistician in order that our appreciation of what we read, see, or hear may be kept in proper perspective.

In the fields of general surgery and the surgical specialties, we have also a source of invaluable information. From the general surgeon, the ophthal-

mologist, the otorhinolaryngologist, the urologist, the orthopedist, the thoracic surgeon, the plastic surgeon, and the neurosurgeon we could derive singular benefit.

Anesthesiology is a specialty so important and vital to us that we should hear at stated intervals the progress it has made. We should adopt the progressive methods and precautions it advocates.

The sensible use of the roentgenologist as a consultant and teacher needs no emphasis. It is important that we know how to ask for and to utilize his modern techniques of diagnosis and therapy.

We also should encourage presentations by good physicists to ensure that we comprehend the advances made in their field as it applies to medicine.

It would be very worth while to hear again the problems of dentistry as they relate to physical and mental health.

The pediatrician can give us valuable aid and information in many of our problems.

Our great problem of prematurity is also one of the pediatrician's great problems. This Association can do much to keep interest high in this serious threat to fetal survival.

It is also time that we began to advance our interest in geriatric medicine and its problems.

There might be quoted in more detail many other aspects of what we might obtain from the workers in the various specialties briefly listed.

The possibility of introducing into our yearly scientific programs two or three papers from these various fields has long appealed to us. The benefits would soon be obvious. We would not only receive but we might in turn give to the men and women who shared in our programs a clear picture of what our problems are. In turn they might then be better enabled to present some of our problems before their own membership and improve their attitude toward and knowledge of the obstetric and the gynecologic patient.

The Association has grown in graceful manner; it has come to a certain maturity which must ensure progressive expression in its meetings. We must present what we do not know in order to know we do not know. We must not stagnate in the pursuit of our repetitious considerations of what we think we know. We should show a deliberate and considered desire to face up to what we do not know.

A condition of perpetual apology for our ignorance is difficult to sustain. The progress of the last thirty years in our specialties must be surpassed in the next twenty years. We should believe in the present with a little doubt, believe in the future with no fear, and know that the past will never come again. We must go to the past for its knowledge and inspiration but we must also bring the past along with us if we hope to progress.

CORTISONE IN TREATMENT OF THE HIRSUTE WOMAN*†

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EXCESSIVE facial or bodily hair growth is an ordeal suffered by a considerable number of women. The advice and assistance of the gynecologist are sought by the hirsute patient because of the cosmetic inelegance or the complicating aberrations in the sexual and metabolic spheres.

In normal females, the pattern of hair distribution varies from individual to individual. Moreover, genetic influences may produce marked deviations in some otherwise normal females. In others, however, the hirsutism is the reflection of some grave endocrine disorder.

Hirsutism, menstrual irregularities, and sterility form a distinctive triad in a fairly large number of apparently healthy women, consequent to some minor disturbance in hormonal balance. This group, in a measure, may be amenable to cortisone therapy. Increased menses, induction of ovulatory cycles, and conception have occurred in several such women as a result of this form of treatment. In a certain number, a slight modification in the hirsutism has been noted.

The hormonal treatment of the hirsute woman should be undertaken only by the gynecologist oriented toward endocrine problems and capable of making a thorough diagnostic study. It is of utmost importance that real endocrinopathies or true disorders be distinguished from constitutional variations. The patients to be treated with cortisone should be meticulously selected. A working classification of hirsutism is outlined in Fig. 1.

Candidates for cortisone administration are those who have an unproved syndrome of increased gonadotropin—probably the luteinizing hormone (LH),[1, 2] or cortical hyperplasia of the adrenal,[3] or those with sclerocystic disease of the ovaries, i.e., the Stein-Leventhal syndrome, and possibly the genetic group.

It may well be that the syndrome of excess LH is the same as the Stein-Leventhal syndrome,[4, 5, 6, 7] neither of which at present can be distinguished from postnatal adrenal hyperplasia.[8, 9] There are protagonists of the excessive gonadotropin theory to account for the syndrome of hirsutism and the theca luteinization observed in enlarged sclerocystic ovaries.[10, 11, 12, 13] The theca-cell hyperplasia[14] of the ovaries seen in patients with mild to extensive virilism

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†Grateful acknowledgment is made to the following pharmaceutical companies for supplies of cortisone needed for this study:

Merck & Co., Inc.: cortisone acetate (Cortone) in tablets, 25 mg., and in saline suspension, 25 mg. per cubic centimeter.

The Upjohn Company: cortisone acetate tablets, 25 mg.

Schering Corporation: cortisone acetate pellets, 100 mg. (Cortogen).

is the result, it has been thought, of excessive gonadotropins, especially LH. In performing gonadotropin assays* in such cases, the assays were moderately elevated in several, and in a few, a positive assay for LH† was obtained by the somewhat inadequate methods presently available.[1] The patients in this series were found to have normal (7-13 mg.) to moderately increased (14-32 mg.) urinary 17-ketosteroid excretion.‡

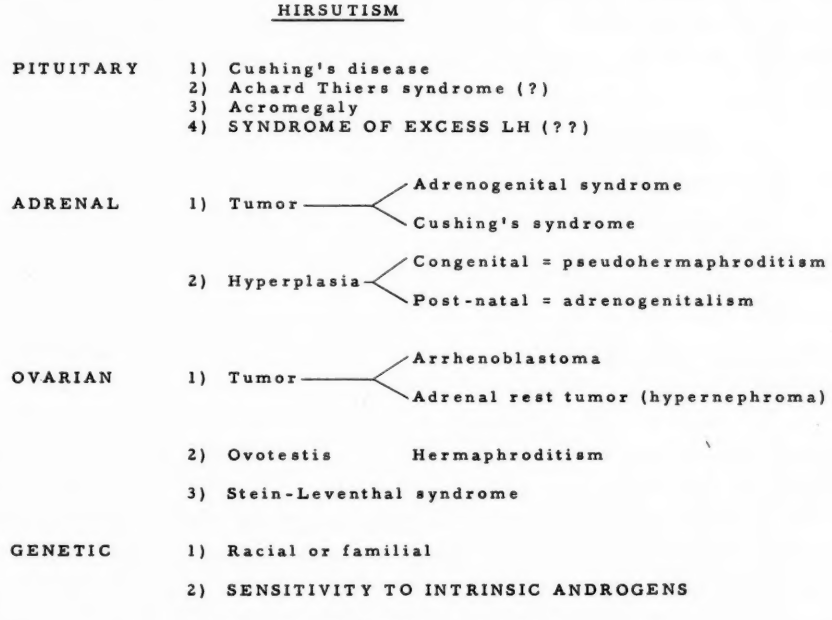

Fig. 1.—Classification of hirsutism.

The Concept of Cortisone Therapy in the Treatment of the Hirsute Woman

The idea that cortisone might be effective in the treatment of hirsutism was first suggested by the work of Whitaker and Baker[15] who found that 17-hydroxy-11-dehydrocorticosterone (Compound E) had an inhibitory effect on hair growth in rats. In 1950, Wilkins and co-workers[16] showed that the administration of cortisone to patients with congenital adrenal hyperplasia caused markedly decreased excretion of 17-ketosteroids and biologically active androgens. These observations suggested to us a possible influence of cortisone upon the hirsute woman who excretes abnormally high amounts of 17-ketosteroids. Accordingly, in 1951, a pilot study was undertaken on a few hirsute, amenorrheic women, using this form of therapy. It was soon found that ovulatory menses occurred in several of these patients. The hirsutism was not materially affected by the relatively short period of therapy of 3 to 4 months. In the

*Urinary gonadotropin (FSH) assays were done by the method described by Klinefelter, H. F., Albright, F., and Griswold, G. C.: J. Clin. Endocrinol. 3: 529, 1943.

†LH assays were done by a modification of the ovarian hyperemia pregnancy test on immature rats (unpublished data).

‡17-ketosteroid assays were done according to the method of Pincus, G.: J. Clin. Endocrinol. 5: 291, 1945.

Cortin (corticoid) determinations were done by the formaldehyde reducing method described by: Daughaday, W. H., Jaffe, H., and Williams, R. H.: J. Clin. Endocrinol. 8: 166, 1948.

meantime, Wilkins and associates[17, 18, 19] reported further on their results with cortisone in the treatment of congenital adrenal hyperplasia, noting that in several of their female pseudohermaphrodites ovulatory menses were induced by comparable doses of cortisone and that there was unquestionable decrease of hirsutism.

Jones and co-workers[3] extended the work of Wilkins by applying the principle of cortisone therapy to hirsute, amenorrheic women, and found that quite a few of these women responded by a decline in the previously elevated 17-ketosteroid excretion, the induction of ovulatory menses, and the occurrence of conception.

Methods of Therapy and Selection of Patients

Twenty-seven patients with varying degrees of hirsutism with or without menstrual irregularities comprise this study. Severe hormonal disorders resulting from Cushing's disease, adrenogenital syndrome, arrhenoblastoma, intracranial lesions, etc., were not included in this study. The ages of our patients ranged from 19 to 39 years. The married patients were either infertile or complained of relative sterility. An arbitrary dose level of 50 mg. of oral cortisone per day was administered continuously for periods of time varying from 2 to 18 months. In a few, the course of therapy was initiated by an intramuscular injection of 100 mg. of cortisone, and, in several, cortisone pellets (six pellets of 100 mg. each) were implanted. The patients were advised to remain on a high-protein, low-carbohydrate, low-fat diet. Thyroid extract, ½ grain per day, was routinely administered to counterbalance any hypothyroidism produced by cortisone. Dietary salt intake was limited and potassium chloride, 5 grains three times a day, was added to the regimen to compensate for excessive urinary excretion of this electrolyte. The patients were checked periodically and urinary assays for 17-ketosteroids and cortins (corticoids) were performed. Urinary gonadotropin assays were done on many of the patients before and after therapy.

The patients were divided into four groups (Table 1) and an analysis of each group yielded the following information:

TABLE I. CORTISONE IN TREATMENT OF 27 HIRSUTE WOMEN

		EFFECT ON MENSTRUAL FUNCTION			
		NO CHANGE	INCREASED NUMBER OF OVULATIONS	INCREASED NUMBER OF MENSES (ANOVULATORY)	VERY MILD IMPROVEMENT IN HIRSUTISM
Amenorrhea	15*	2	8	3	4
Irregular menses	6	2	4	-	1
Regular menses	4	4	-	-	1
Hysterectomized	2	-	-	-	2

*Discontinued in two patients because of untoward results.

Group 1. Hirsutism With Amenorrhea.—The largest group, comprising 15 patients, complained of hirsutism and amenorrhea. The patients in this group varied considerably in the degree of hirsutism and frequency of menses. The amenorrheic episodes varied from 2 to 26 months. In this group, 5 had ovarian resections before institution of cortisone treatment, and 2 had resections

subsequent to cortisone therapy. In 2 cases the cortisone was discontinued within 1 to 2 months because of untoward effects such as depression and melancholia. Of the remaining 13 patients, marked improvement in frequency of ovulatory menstruation occurred in 6, 2 of whom became pregnant. Three of the patients in this group were unmarried, and hence information as to the effect on sterility will have to await a more propitious time. In 2 patients occasional ovulation has occurred. In 3 there has been increased frequency of menstruation, without ovulation. In 2 patients, no change took place.

Group 2. Hirsute Women With Irregular Menses.—Six hirsute patients with a previous history of only slight irregularity in menstrual function have been on cortisone for periods varying from 3 to 8 months. More regular menstruation has followed in 4. Little improvement has been noted in the other 2 thus far. One patient in this group who has received medication for 8 months claimed slight slowing down in the rate of hair growth. It is worth mentioning that in one patient the life of the corpus luteum, which was short lived (4 to 5 days as noted by the basal temperature record), was prolonged to a normal 14 to 16 day luteal phase.

Group 3. Hirsute Women With Regular Menses.—Of these patients, 3 had regular menses and cortisone was administered purely for its effect on the hirsutism. Two of the patients in this group discontinued treatment after 4 months because it appeared to be without effect. The third patient has continued cortisone for 7 months and recently has noted some improvement in facial and bodily hair growth, i.e., it seems to be growing more slowly, and the hair on her head, which had become alarmingly thin, has become thicker. Menstruation was not disturbed in any of these patients. Included in this group is a fourth patient who had an ovarian resection performed approximately 15 months previously because of functional amenorrhea and hirsutism. Following the resection, ovulatory menstruation followed but the hirsutism remained the same. She was placed on cortisone and after several months of therapy a slight decrease in rate of hair growth was claimed by the patient.

Group 4. Hirsute Women Previously Hysterectomized.—One hirsute patient who had a hysterectomy performed some 10 years previously had palpably enlarged ovaries (probably the Stein-Leventhal syndrome). She has been under treatment for 16 months and shows only slight modification of the hirsute condition. Improvement in her general well-being has been marked. A second patient, who had a hysterectomy and bilateral ovariectomy because of adenoacanthoma of the endometrium (who also had typical sclerocystic ovaries of the Stein-Leventhal syndrome), has received 1,700 mg. of cortisone (Fig. 5) and shows some lessening in rate of hair growth. Whether this is due to the cortisone treatment or to the ovariectomy has not been decided.

Comment

Why is cortisone effective in inducing ovulatory menses in some hirsute amenorrheic patients? A complete and satisfactory answer to this and similar questions on the mechanism of action cannot be made at this time. However, the following observations seem pertinent to the question.

Many investigators have shown that cortisone is effective in reducing 17-ketosteroid excretion (Fig. 2). However, increased production of androgen-like hormones, as evidenced by an increased excretion of 17-ketosteroids, is not the prime factor responsible for amenorrhea, though this mechanism may be directly responsible for hirsutism, since elevated 17-ketosteroid excretion levels are present in hirsute women who have cyclic ovulatory menses.

Cortisone may produce its effect not merely by depressing adrenocorticotropin (ACTH) production but by so modifying pituitary activity as to permit a more orderly release of pituitary gonadotropins. This modifying effect of cortisone on pituitary activity possibly may be brought about by a balancing action of growth hormone and adrenal steroids. The concept of release of pituitary gonadotropins finds support in the work of Sohval and Soffer[20] who have shown that the administration of ACTH or cortisone causes an immediate elevation of urinary gonadotropin titers. Furthermore, Davis and associates[21] administered ACTH to 13 amenorrheic patients and episodes of uterine bleeding were induced in 9 of these. In some, bleeding occurred in spite of the rise in 17-ketosteroid and cortin excretion. Moreover, in 1948, Forsham and collaborators[22] reported that three amenorrheic patients who had not menstruated during the year menstruated six to ten days after a single injection of 20 mg. ACTH. It should be mentioned, too, that Farnsworth[23] reported temporary re-establish-

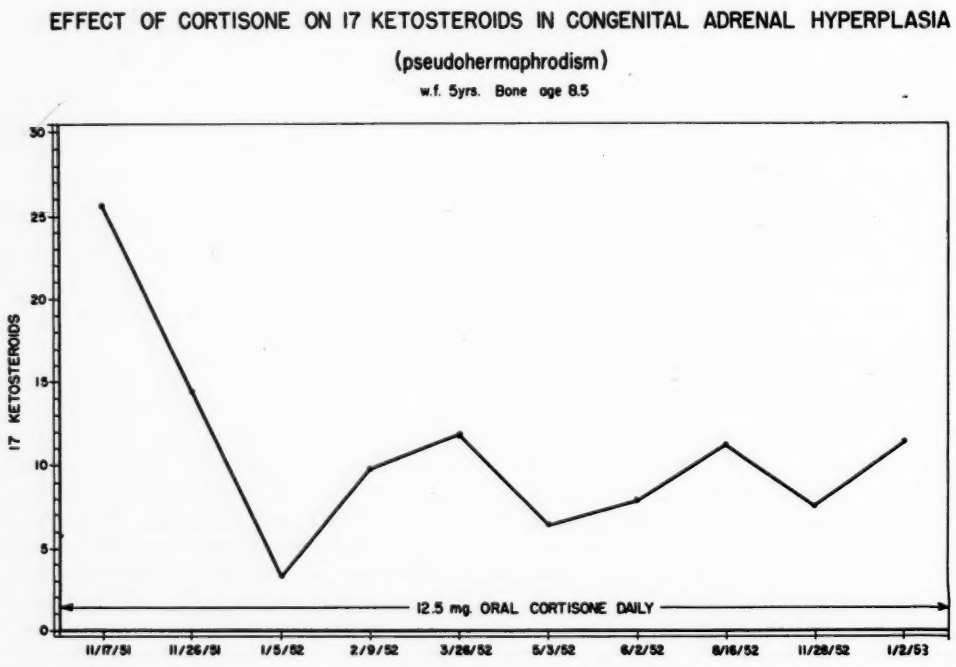

Fig. 2.—Note marked reduction 17-ketosteroid excretion in a 5-year-old patient with congenital adrenal hyperplasia (female pseudohermaphroditism) on 12.5 mg. cortisone per day.

ment of regular menses in a 23-year-old amenorrheic girl with nephrosis following treatment with ACTH. These observations would seem to indicate that ACTH or cortisone administration depresses pituitary corticotropin activity and thus permits a better balance in production and secretion of other pituitary hormones, and that in certain cases the effectiveness of cortisone is not dependent upon reduced androgen and/or estrogen secretion by the adrenals (Wilkins' hypothesis).

In an effort to clarify the possible physiologic role of cortisone, certain cases were selected from our series for critical analysis because of significant findings.

CASE 1 (Fig. 3).—The patient was a 26-year-old amenorrheic woman who was mildly hirsute and infertile. Her urinary 17-ketosteroid excretion was not influenced to any marked degree by 50 mg. of cortisone daily. She, nevertheless, after a 2 year period of amenorrhea, began to have episodes of uterine bleeding soon after cortisone therapy. This patient was treated continuously from February, 1952 and conceived 10 months later. In that period of time she had eight episodes of uterine bleeding of which six were ovulatory in type as determined by basal temperature records.

It seems, then, that this 26-year-old patient who had had functional amenorrhea since the age of 13, having none or no more than two menstrual periods in any one year, probably experienced some type of pituitary release through the depressing action of cortisone on pituitary corticotropins, even though this dosage level of cortisone failed to influence materially the range of 17-ketosteroid excretion.

The question may be asked, "What role does adrenal dysfunction or mild hyperfunction play in the so-called Stein-Leventhal syndrome of hirsutism, amenorrhea, and sterility?" Many of these patients have increased urinary

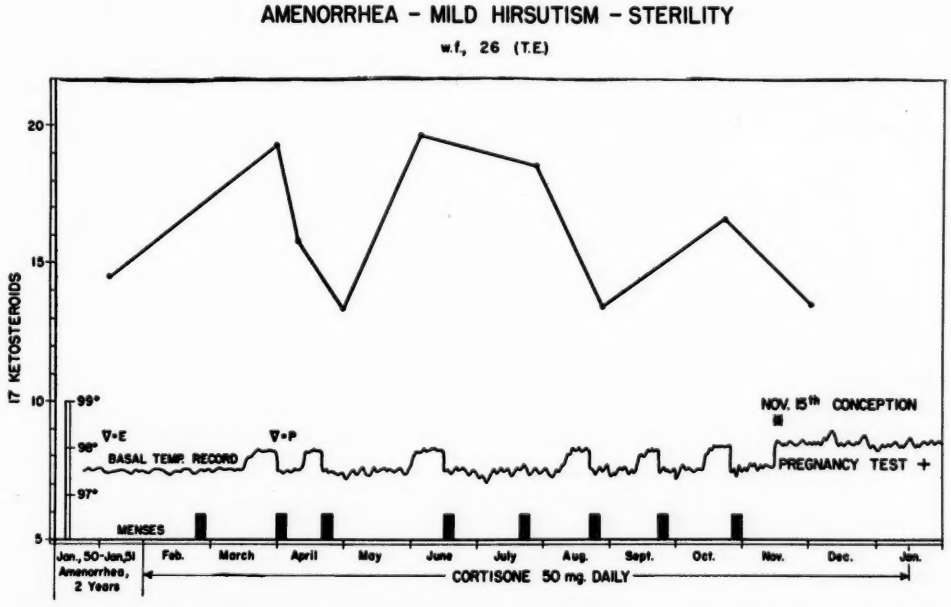

Fig. 3.—The influence on 17-ketosteroid excretion of 50 mg. cortisone per day in this amenorrheic patient with mild hirsutism and sterility was erratic. However, induction of menses followed a 2 year amenorrheic period, with frequent ovulatory menses and conception.

17-ketosteroids. Does the increased 17-ketosteroid excretion come from the enlarged microcystic ovaries (hyperthecosis) or from the adrenals? Is this syndrome primarily a pituitary disturbance with resultant imbalance of the pituitary-adrenal-ovarian axis, or is it primarily an ovarian disturbance with secondary imbalance in the pituitary-adrenal axis? Perhaps an inkling as to the answer to the point in question may be found in a study of Fig. 4.

CASE 2 (Fig. 4).—The patient was an amenorrheic, hirsute woman aged 32 years, who had been menstruating on the average of about three times per year. Positive findings included palpably enlarged ovaries, marked hirsutism of face, breast, abdomen, and thighs.

There were no enlargement of the clitoris, and no voice changes. Her blood pressure was normal and her vaginal smear showed a three-plus estrogenic effect. Her urinary 17-ketosteroids were elevated, i.e., 30 and 32 mg. per 24 hours. After bilateral ovarian resection of typically enlarged sclerocystic ovaries (large, pale ovaries), menses occurred at intervals of about every 2 months during the following 16 months. There was no diminution in hirsutism although 17-ketosteroid excretion fell to a level of about 20 mg. plus per 24 hours. When cortisone, 50 mg. orally per day, was started toward the end of August, 1951, the patient soon noted a greater regularity in uterine bleeding episodes. Basal temperature records, which she now kept, showed that she had 13 ovulatory menses in the 16 month period of cortisone therapy. The 17-ketosteroid levels fell to values varying from 10 to 19 mg. There was now noted a lessening, though not very great, of the hair growth.

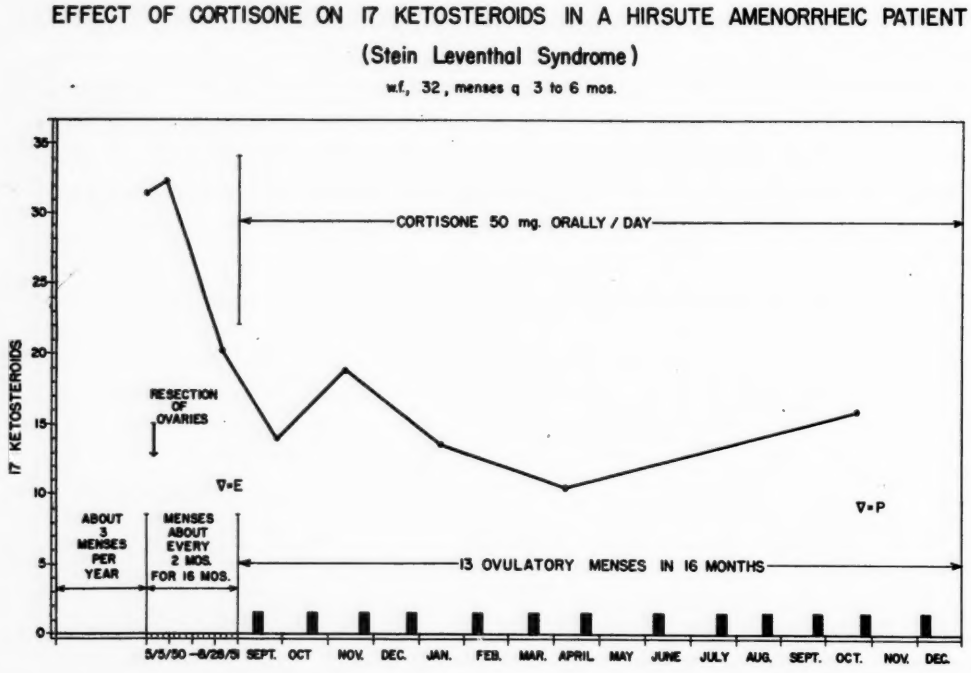
EFFECT OF CORTISONE ON 17 KETOSTEROIDS IN A HIRSUTE AMENORRHEIC PATIENT
(Stein Leventhal Syndrome)
w.f., 32, menses q 3 to 6 mos.
17 KETOSTEROIDS
CORTISONE 50 mg. ORALLY / DAY
RESECTION OF OVARIES
▽=E
▽=P
ABOUT 3 MENSES PER YEAR
MENSES ABOUT EVERY 2 MOS. FOR 16 MOS.
13 OVULATORY MENSES IN 16 MONTHS
5/5/50 - 8/28/51 SEPT. OCT NOV. DEC. JAN. FEB. MAR. APRIL MAY JUNE JULY AUG. SEPT. OCT. NOV. DEC.

Fig. 4.—Ovarian resection was followed by lowered 17-ketosteroid levels and induction of more frequent menses. However, following treatment with 50 mg. of cortisone orally per day, menses became more regular and ovulatory in nature with further reduction in 17-ketosteroid excretion.

It seems that, by ovarian resection, a modification in the pituitary-ovarian axis followed as manifested by some lessening of 17-ketosteroid excretion and more frequent menses, but that when cortisone was administered a further modification in pituitary-adrenal-ovarian axis occurred, since 17-ketosteroid excretion dropped further, menses became quite regular and ovulatory, and the degree of hirsutism was modified.

Perhaps a significant role is played by the enlarged microcystic ovaries in the production of hirsutism. An analysis of Case 3 (Fig. 5) offers some evidence.

CASE 3 (Fig. 5).—This case is that of a markedly hirsute 28-year-old patient who had amenorrheic episodes followed by bouts of uterine bleeding. Palpably enlarged ovaries were present and these were demonstrated by roentgenography. She was seen after she had been bleeding for several weeks. Suction curettage was done and bleeding was readily controlled by

combined estrogen and progesterone therapy, and this was followed by a normal withdrawal period. On June 3, 1952, 100 mg. of cortisone was given intramuscularly and 6 pellets of 100 mg. each of cortisone acetate were implanted subcutaneously. Twenty-five mg. of cortisone orally per day was added from July 1 to Aug. 10, 1952. Suction curettage revealed adenoacanthoma of the endometrium but, because of the excellent control of the bleeding, it was decided to wait for further confirmation of the diagnosis by repeat endometrial biopsies. In the meantime, 17-ketosteroid studies revealed a fall in levels from 23 mg. per 24 hours to values of 12 to 14 mg. per 24 hours. Panhysterectomy was performed on Aug. 20, 1952. The ovaries were typical of the Stein-Leventhal syndrome. The uterus on histopathologic examination revealed adenoacanthoma confined to the endometrium without invasion of the body of the uterus. After ovariectomy, the 17-ketosteroids fell further to values ranging from 6 to 11 mg., and considerable modification of hair growth was noted.

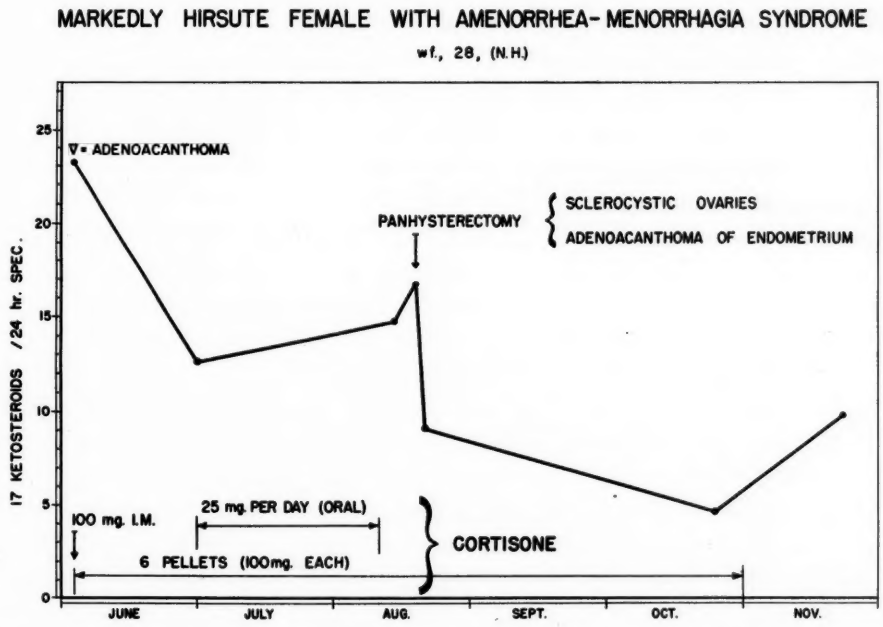

Fig. 5.—Cortisone treatment lowered 17-ketosteroid excretion. However, following panhysterectomy, the 17-ketosteroid excretion fell still further.

The question must be asked, "Were the ovaries the important source of androgen production, since cortisone definitely lowered the titer but ovariectomy lowered it still further?" In evaluating the last two cases it would seem that the ovaries probably are responsible for part of the 17-ketosteroid production and that the hyperthecosis so frequently seen on histologic study of the ovaries may be the result of excess pituitary stimulation of the ovaries—probably of LH. It may well be, then, that the syndrome of Stein-Leventhal results from excess pituitary LH with resultant enlargement of the ovaries, and that the ovaries are in a good measure responsible for the increased urinary 17-ketosteroids found in many of these cases. This may account for the fact that cortisone often fails to benefit the true case of Stein-Leventhal syndrome while it is frequently effective in patients with increased 17-ketosteroid production caused by adrenal hyperplasia.

Summary and Conclusions

From the data derived from a study of 27 hirsute women, it appears that the prolonged administration of cortisone may modify the rate of bodily hair growth.

Of the patients with menstrual disorders, some may respond by cyclic ovulatory menses and ultimate conception, others simply by increased number of menstrual periods, many of which may be anovulatory, while other patients may show no improvement.

In comparing these cases with our previous experiences in the treatment of hirsute amenorrheic women by ovarian resection, it appears that the patients who experienced little benefit following surgery were significantly aided by further cortisone therapy. On the other hand, some of the patients who failed to respond to cortisone were benefited by ovarian resection. If one can draw conclusions from this small series of patients, it might appear that there are different types of cases—those in whom the disorder is primarily ovarian, others in whom it is primarily adrenal, and others in whom there is an imbalance in the pituitary-adrenal-ovarian axis.

The finding of hirsutism, menstrual disorders, and mild to moderate elevation in urinary 17-ketosteroids may be common to most cases in these groups; nevertheless, it is difficult to classify them categorically as belonging to one or another group. It is our impression that excess androgen production in these cases may come from either the excessively luteinized (hyperthecosis) ovaries or from the adrenal cortex or from both sources. If this concept is acceptable, it would explain why cortisone helps one group, ovarian resection another, and combined methods help a third group.

The physiologic role of cortisone in the management of the hirsute woman may have its effect not merely by depressing 17-ketosteroid excretion through its inhibition of adrenocorticotropin (ACTH) production, but by a balancing action of growth hormone and adrenal steroids so as to permit a more orderly release of pituitary gonadotropins.

While we regret that our facilities do not permit a more nearly complete presentation, perhaps some of the observations made in this preliminary study may furnish a few clues and stimulate further studies on this intricate and perplexing problem.

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Discussion

DR. FRANK R. LOCK, Winston-Salem, N. C.—The question of whether or not hirsutism represents a pathologic condition is often of more importance than its treatment. We find that the diagnosis of possible masculinization is often applied to young women who are menstruating regularly and have recently had children, because of the presence of a moderate amount of facial hair. At the other extreme was a patient with male pseudohermaphroditism, who had no feminine characteristics except a genital defect which made coitus as a female possible. This man was a successful woman who taught in high school and was happily married to a successful businessman. One undescended testicle had been removed at the time of repair of an inguinal hernia; the other remained. The patient was referred for treatment because of an abundant beard and mellow bass voice. It is obvious that no masculinizing ovarian tumor was suspected after a history and physical examination revealed the true character of the problem. As a matter of fact, the patient and husband were not given a diagnosis in view of the entirely satisfactory social and marital relationship which existed.

Dr. Greenblatt's observations upon the use of cortisone in reducing 17-ketosteroid excretion in hirsute women provide additional evidence of some value of this agent in the treatment of patients with abnormal adrenal activity. Wilkins used this hormone in pseudohermaphroditism resulting from congenital adrenal hyperplasia, and observed that ovulatory menses were induced following its administration. This change was preceded by a reduction in the levels of 17-ketosteroid excretion.

G. E. S. Jones and her associates have made similar observations which were recently reported to the American Society for the Study of Sterility. She used low-dosage cortisone therapy and produced ovulatory menses in a group of patients with follicular-phase failure related to apparent mild adrenal dysfunction. She considered patients as potentially responsive who had amenorrhea or oligomenorrhea, hirsutism, acne, and slightly elevated 17-ketosteroid excretion. Three of 6 patients with the Stein-Leventhal syndrome were improved following cortisone treatment.

There is no clear understanding of the mode of action of cortisone used for the treatment of menstrual abnormalities. It appears, however, that it may be effective when the problem is related to adrenal dysfunction and ineffective in patients with normal adrenal function. In any event, the evidence now accumulating offers some hope of satisfactory treatment of a group of patients with whom we have had no success in the past.

DR. PABLO TABIO, Havana, Cuba (by invitation).—The occurrence of hirsutism in women during late adolescence or early adult life presents a common and difficult problem for the endocrinologist. In many instances there are no symptoms except hirsutism.

The menses may be irregular and amenorrhea may occur. The excretion of 17-ketosteroids is frequently moderately elevated, 15 to 25 mg. per day. However, in other cases the output is within the normal range for females or at the male level (10 to 15 mg.).

The occurrence of progressive virilization, the development of symptoms of Cushing's syndrome, or the finding of a high output of 17-ketosteroids is an indication for adrenal exploration in the hope of finding an operable tumor. A careful pelvic examination should be made first to exclude the presence of an arrhenoblastoma. However, the results of adrenal exploration are often disappointing and may fail to shed light on the etiology. Frequently neither tumor nor definite hyperplasia of the adrenal can be demonstrated even with biopsy and microscopic examination.

In cases in which the 17-ketosteroid excretion is elevated it seems probable that there is an excessive activity of the adrenal in spite of the absence of hyperplasia. A normal output of 17-ketosteroids may suggest that some genetic or constitutional factor may be responsible for an increased sensitivity of the hair follicles to androgen.

We must also rule out in these cases of hirsutism and amenorrhea the Stein-Leventhal syndrome. The characteristics of this syndrome are menstrual irregularity featuring amenorrhea, a history of sterility, hirsutism, and, less consistently, retarded breast development and obesity. On exploration these patients are found to have large polycystic ovaries with thickened capsules. Microscopic examination shows evidences of FSH activity but lack of ovulation and corpus luteum formation.

Most workers question the explanation that the failure of ovulation is due to the thickened ovarian capsule. The possibility that this ovarian condition might be caused by increased androgen activity of the adrenal has not been excluded. However, Ingersoll and McDermott observed at the Massachusetts General Hospital, in a series of 21 cases of Stein-Leventhal syndrome, that hirsutism occurred in 9 of their patients. The possibility that there might be some associated adrenal abnormality or androgen-secreting tumor led them to determine the 17-ketosteroids output in these 9 patients, and in no instances was there an increase over the normal female level. Perhaps the mechanical disorder in the ovary results in a shift in the estrogen-androgen balance which we are unable to measure accurately at present.

A new and interesting observation suggests that cortisone administration may be useful in these patients. We all know that excessive amounts of estrogen and androgen of the adrenal inhibit the secretion of pituitary gonadotropins (FSH), so that the ovaries are not stimulated to secrete estrogen. Cortisone therapy inhibits the effects of ACTH on the adrenal, diminishing its secretions. The decrease of excessive androgen and estrogen of the adrenal releases the normal pituitary ovarian mechanism.

We are in fact starting to treat a few amenorrheic patients with cortisone, but it is too early to arrive at a conclusion. Nevertheless observation leaves no doubt that these few patients showed a definite decrease of hirsutism.

The vaginal smear becomes estrinized and the hirsutism decreases progressively. To obtain the most satisfactory results, it is essential to give the minimum amount of cortisone necessary to maintain the excretion of 17-ketosteroids below 8 mg. per day in the older patients. It is obvious that it is desirable to give the smallest effective dose of cortisone in order to avoid as much as possible the risk of abnormal metabolic or toxic effects.

EXPERIENCE OF THE SAVANNAH TUMOR CLINIC IN CARCINOMA OF THE STUMP OF THE CERVIX*

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(From the Savannah Tumor Clinic)

CARCINOMA of the cervical stump is a condition which can and should be almost completely eradicated. Total hysterectomy can be accomplished in practically all cases where removal of the uterus is indicated. In the few remaining cases where supracervical hysterectomy must be done, careful evaluation of the cervix by biopsy or cytological studies, both before and following surgery, will usually suffice as adequate prophylaxis.

In a recent review of the literature from 1941 to 1951, Braun and Green[1] found 318 reported cases of carcinoma of the cervical stump. They reported 43 additional cases which comprised 13 per cent of the total of cervical carcinomas seen in their clinic.

Cervical stump carcinoma gives a poorer prognosis for the patient than carcinoma of the cervix arising in an intact uterus because of two factors. First, it is more difficult to give adequate radium dosage, because of the short endocervical canal and the closer proximity of the bladder. Second, the patient who has had a supravaginal hysterectomy develops a false sense of security, and many times ignores early symptoms of carcinoma which, if investigated, might well lead to detection of carcinoma in its early stages.

The Savannah Tumor Clinic is in many ways unique. It is an outgrowth of a clinic which was established in 1938 as a part of the so-called State Aid program of the Georgia Public Health Department. These clinics were established as diagnostic and treatment centers to which were referred medically indigent patients from several surrounding counties.

At the present time there is no hospital in Savannah large enough to house such a clinic and by 1947 the clinic had outgrown the facilities in the Health Center. In addition there was insufficient high voltage x-ray equipment and personnel to treat the patient load adequately.

Accordingly, in 1947, through the efforts of a few members of the profession and interested laymen, a nonprofit corporation was formed, adequate quarters constructed, and new equipment purchased. The services of a full-time radiation therapist were acquired, and the clinic was set up to operate in full cooperation with the medical profession, the existing hospitals, pathological laboratory, the American Cancer Society, and the Cancer Division of the State Health Department.

One unique feature of the clinic is that no patients are admitted except by referral from a doctor. All patients are seen either for diagnosis or

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treatment without regard to financial status. Fees are based on ability to pay. Where surgery is to be combined with radiation therapy, the referring surgeon is permitted to treat his patient if he wishes. Surgery on indigents is done gratis by the clinic staff.

The other unique feature is that the professional work of the clinic is under full control of a committee composed of five members of the local Medical Society elected by the Medical Society. Finances are governed by a board of doctors and laymen. Funds are received through fees, payments by the state under the State Aid program, and private donations. The annual deficit is met by Community Chest funds.

This report deals with data secured from patients seen in the Savannah Tumor Clinic for a period of 14 years, 1938 through 1951. During this time a total of 217 patients with biopsy diagnosis of cervical carcinoma were treated, and of this group 18 had carcinoma arising in the cervical stump. Thus 8.3 per cent of all the cases treated had carcinoma following supracervical hysterectomy, and it is interesting to note that none of these had a biopsy of the cervix prior to surgery.

An attempt has been made to classify these cases according to the development of the carcinoma in relation to the time supracervical hysterectomy was done. Cosbie[2] is of the opinion that if carcinoma develops within three years following supracervical hysterectomy, the neoplasm was present and demonstrable at the time of surgery and classifies it as coincidental. Ward[3] is of the opinion that if carcinoma develops clinically within one year of surgery, the lesion is coincidental. Since it is a debatable matter whether the cancer is coincidental or develops subsequent to surgery we have divided the cases into three groups as shown in Table I.

TABLE I. TIME CARCINOMA DETECTED IN RELATION TO SURGERY

	AT SURGERY	ONE YEAR FOLLOWING SURGERY	OVER ONE YEAR FOLLOWING SURGERY
Number of Cases	6	3	9
Percentage	33%	17%	50%

The first group comprises the cases where carcinoma was definitely present at the time of surgery proved by microscopic evidence of carcinoma in the surgical specimen removed. There were 6 cases in this group and all cases could have been easily diagnosed prior to surgery.

The second group is composed of those cases where clinical and pathological evidence of carcinoma was present within one year following surgery. Three cases, or 17 per cent, fall into this group, and we feel that clinical evidence of carcinoma was probably present in these cases also at the time of surgery.

It is our opinion that since cytological methods have been added to our armamentarium in diagnosing early neoplastic disease of the cervix, the first

two groups should be considered as coincidental cases. Using this criterion, 9 cases, or 50 per cent of the total stump carcinomas, were present and easily demonstrable at the time surgery was done.

In the third group are placed all those cases where clinical and pathological evidence of carcinoma was detected over one year following surgery. There were 9 cases, or 50 per cent, in this group which should be considered sequential carcinoma. All of these 9 cases were detected over eight years following surgery.

The pathological aspects of the carcinomas encountered are listed in Table II. There were 10 squamous-cell carcinomas, 5 adenocarcinomas, and 3 undifferentiated carcinomas. Using the League of Nations classification, 4 were Stage I, 4 Stage II, 3 Stage III, and 7 Stage IV.

TABLE II. CLINICAL CLASSIFICATION OF CARCINOMA OF CERVICAL STUMP

TYPE	STAGE I	STAGE II	STAGE III	STAGE IV	TOTAL
Squamous-cell	3	1	2	4	10
Adenocarcinoma	1	1	1	2	5
Undifferentiated	0	2	0	1	3
Total	4	4	3	7	18

The most significant feature of this tabulation is the 10 cases of carcinoma first seen in Stages III and IV, thus putting 55 per cent of the cases in a relatively incurable category. The 5 cases of adenocarcinoma of the endocervical canal bring to light another feature of great importance. A large number of carcinomas of the endocervical canal will be missed by routine biopsy at the squamocolumnar junction, and the best diagnostic method to arrive at a diagnosis of early adenocarcinoma is curettage of the endocervical canal. This is a relatively easy office procedure and should be done prior to surgery in all cases where the cervix is to be left intact.

Howard and his associates[4] in a study of 400 uteri removed for noncervical diseases found 1.8 per cent cases of metaplasia with areas of atypical cells and 3.5 per cent cases of intraepithelial carcinoma. This represented a total of 21 cases, or 4.3 per cent, with abnormalities or intraepithelial carcinomas. They concluded from this study that most of the cases had their origin in the endocervix rather than in the portio vaginalis. Pund and Auerbach[5] had previously published similar conclusions.

TABLE III. STAGE CARCINOMA DETECTED IN RELATION TO SURGERY

	STAGE I	STAGE II	STAGE III	STAGE IV
Coincidental	1	2	1	5
Sequential	3	2	2	2

In Table III, the cases have been separated so that the stage of the neoplastic process is shown in relation to the time elapsed since the supracervical hysterectomy was done. The 6 cases of Stage III and Stage IV malignancy found in the coincidental group reflect poor diagnostic methods on the part of the surgeon. The 4 cases of sequential carcinoma in Stages III and IV bear

out the point that patients who have had hysterectomy develop a false sense of security and neglect early symptoms which would lead to earlier diagnosis.

The clinical course of the stump carcinomas has been divided into the survival time after treatment of the coincidental and sequential cases, as shown in Table IV. A total of 8 deaths have occurred of which 6 were in the coincidental and 2 in the sequential group. All of these deaths occurred less than three years following therapy. Of the 10 living patients only 2 have survived over five years and these are in the sequential group. Three of the living patients have extensive and incurable Stage IV carcinomas at present and these are in the survival time under three years.

TABLE IV. CLINICAL COURSE FOLLOWING TREATMENT

	LIVING			DECEASED		
	1 YEAR	2-5 YEARS	OVER 5 YEARS	1 YEAR	2-5 YEARS	OVER 5 YEARS
Coincidental	1	2	0	6	0	0
Sequential	2	3	2	1	1	0
Total	3	5	2	7	1	0

The method of treatment of stump carcinoma at the Savannah Tumor Clinic has been combined radium and x-ray therapy. Since each treatment will have individual variations depending on the stage of the cancer, weight of patient, accessibility of the cervical canal, and many other factors, an average type therapeutic regimen is given as an example for a Stage II carcinoma.

1. *Insertion of radium first* for both local and parametrial effect. In Stage II this does not exceed 76.33 mg. of radium salt for 72 hours. (This total amount of radium given with these factors produces, by experience, only extremely rarely any radium complications; but if a larger amount is used for a shorter period, complications will develop.)

2. *X-ray therapy* without a waiting period using seven ports, six pelvic and one vaginal, giving six pelvic ports 200 r per port, treating two fields daily, five days weekly, for a total per port of from 1,800 to 2,400 r, and using 0.5 mm. copper, or 0.25 mm. copper plus 0.2 mm. tin filter at 50 cm. target skin distance. Following the six pelvic ports one vaginal direct port is used in doses varying from 300 to 500 r, depending on the amount of tumor present, for a total of about 1,800 to 2,100 r.

Summary and Conclusions

1. Eighteen cases of carcinoma of the cervical stump are presented. These cases comprise 8.3 per cent of the total cases of cervical carcinoma seen in an eight-year period.

2. Nine cases are listed as coincidental carcinoma, present at the time of surgery, and 9 cases are listed as sequential carcinoma.

3. Ten cases are classified as League of Nations Stage III and Stage IV when first diagnosed.

4. Eight deaths have occurred and 6 of these were in the coincidental group. Of these cases only one patient lived longer than one year following therapy.

5. A plea is made for total hysterectomy in preference to the supracervical type, and a thorough search for carcinoma in all cases where the cervical stump must be left intact.

Addendum.—Since this material was prepared two more cases were found during the last weeks of 1952. Both were in the sequential group and both are Stage I squamous-cell carcinoma. Since there were 39 cases of carcinoma of the cervix found in 1952, the addition of these cases gives an over-all incidence of 7.8 per cent.

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Discussion

DR. TOMAS ARMSTRONG, Havana, Cuba (By invitation).—The best way to eliminate this disease is to perform total hysterectomy in all patients in whom removal of the uterus is indicated. Radium, x-ray therapy, and surgery are far from a perfect treatment for cancer. We use them because they are the only hope we have for patients with malignant disease, but we feel much more sure when we can prevent the incidence of a cancer entirely.

Years ago, most of our surgeons and gynecologists did not as a rule like to perform total hysterectomies. We have been more conservative than our friends from North America. We performed many subtotal hysterectomies, some myomectomies, and now and then a fundal hysterectomy, and also a Cirio's myometrectomy, leaving in these last cases some amount of endometrial tissue. When we were too radical, our patients suffered for years on account of hormonal and other genital disturbances. To our women, especially the younger ones, it is something of importance for them to continue menstruation after their operations, no matter if it is only a very scanty period.

Now that we have good hormonal products and have also learned the danger of leaving a cervical stump, our better gynecologists perform more total hysterectomies on their patients. I personally leave the cervix only in some younger women, always after a Schiller test, a careful cytological study of the vaginal smear, and a biopsy curettage of the cervix.

I present to you in Table I the number of abdominal hysterectomies that were performed in the last four years by the twenty-two different surgeons who work in the Emergency Hospital, the Free City Clinic of Havana. If we add the vaginal hysterectomies and we take the record only of the operations performed by the best-trained gynecologists of the Hospital, I am sure the rate of our subtotal hysterectomies would have been lower.

TABLE I

	SUBTOTAL HYSTERECTOMIES	TOTAL HYSTERECTOMIES
1949-1950	288	248
1951-1952	240	254

In Table II we present the results that were obtained from the 4,499 vaginal smears that we made in the last eight years. Dr. Leon Blanco made the correct diagnosis of cancer in 182 patients (4.08 per cent of the total number).

TABLE II

Total No. of patients	4,499	
Positive cancer	182	(4.08%)
Wrong positive diagnosis	12	(0.26%)
Wrong negative diagnosis	7	(0.15%)

In Table III we can see the correct diagnosis in the patients who had false positive diagnoses at the first examination.

TABLE III

False positive diagnosis	12
Correct diagnosis:	
Trichomoniasis	4
Metaplasia of endocervix	3
Senile colpitis	2
Cervicitis	3

In Table IV we show the cases in which we missed the diagnosis of cancer that was later confirmed by a biopsy or by operation and a correct anatomic study.

TABLE IV

False negative diagnosis	7
Correct diagnosis:	
Infiltrative cancer of the cervix	2
Endometrial cancer	5

Finally, in Table V we present a more detailed study of our positive cases confirmed by an anatomic postoperative study.

TABLE V

Surface cervical cancer		168	(92.3%)
In situ	27		
Infiltrative	141		
Endocervical cancer		2	(1.09%)
Endometrial cancer		11	(6%)
Choriocarcinoma		1	(0.05%)

I am sorry that I cannot tell you how many of these 170 cases of cervical cancer are of the cervical stump. In a rapid review I found 2 stump cancers in 50 cervical cancers that I looked over. They represented 4 per cent of the cervical cancers, less than the 7.8 per cent reported by Dr. Kelley and Dr. Brawner. Of course, our percentage has not the same value since it was obtained from only 50 cases.

It would be interesting if Dr. Kelley and Dr. Brawner could inform us what percentage of their subtotal hysterectomies have recently shown a cancer of the stump. For us this study is very difficult because our people do not come to be checked while in good health, and, as a rule, we see the cervical stumps only when there is cancer or some other disease.

DR. CHARLES J. COLLINS, Orlando, Fla.—Again the evidence, so ably presented by Dr. Kelley and Dr. Brawner, mounts to incriminate the cervical stump as a menace to the patient who has had an incomplete hysterectomy. Let us hope time will soon relegate it to the past where it belongs.

I wish to discuss our experience with this type of preventable cancer at the Orange Memorial Hospital. From 1946 through 1952, 259 patients with cancer of the cervix were admitted to the hospital. Twenty, or 7.8 per cent, had incomplete hysterectomies in the past. This is the identical incidence found by the essayists. If the three-year interval between the hysterectomy and the diagnosis of the cervical stump cancer be accepted as evidence that the cancer was present at the time of hysterectomy, 4 cases can be excluded, giving an incidence of 6.2 per cent. The longest interval between the operation and the diagnosis of the disease was 28 years. It was interesting to note that 4 patients were in the 25 to 28 year interval.

The staging of the cancer showed 1 case in Stage 0, 4 in Stage I, 9 in Stage II, 2 in Stage III, and 4 in Stage IV. The youngest patient was 34 years of age and the

oldest 68 years. Seventy per cent were within the 40 to 60 year group. There were no adenocarcinomas of the endocervix in this series. All were of the squamous-cell type.

The treatment was somewhat more diversified than the routine use of radium and x-ray as reported by Dr. Kelley and Dr. Brawner. One patient received no treatment and two had only palliative urinary diversion procedures. Vaginal excision of the stump was employed in one case, and in another the same with postoperative x-ray. Abdominal radical lymphadenectomy with excision of the stump was done in one patient and 12 received radium and x-ray. The patient with vaginal excision of the stump alone showed invasive Stage I cancer and was inadequately treated.

No five-year salvage rate can be given as this review covered only the last six years. If the results in the treatment of these patients equaled those of carcinoma of the cervix as a whole, which they undoubtedly will not, the most optimistic projected five-year salvage would be 9 patients, or 45 per cent. Excluding the 4 cases with probable cancer at the time of hysterectomy, this rate would drop to 38 per cent. Thus it may be estimated that if these 16 patients had received complete instead of incomplete hysterectomy, it would have been necessary for the operative mortality to have been at least 62 per cent to have obtained the same ultimate salvage.

Since education of the patient in cancer prevention cannot influence the choice between complete and incomplete hysterectomy in the management of benign disease of the uterus it seems that this education must be directed toward the surgeon. That this can be done is evidenced by an evolution in the types of hysterectomies done in our hospital. From 1947 to 1952 the complete operation had increased from 34 per cent to 62 per cent, the vaginal from 20 per cent to 31 per cent, and the incomplete had decreased from 46 per cent to 7 per cent. Over 30 per cent of the hysterectomies are still done by general surgeons in the Orange Memorial Hospital.

Perhaps we are overlooking a valuable means of cancer prevention in not advocating the vaginal removal of all cervical stumps. The incidence of cancer is about 2 per cent and the best five-year survival rate is about 40 per cent. There is then a calculated mortality of around 1.2 per cent in all women who carry cervical stumps. The operative mortality should be insignificant in the vaginal removal of these stumps by gynecologists trained in vaginal surgery.

MIXED MESODERMAL TUMORS OF THE UTERUS*

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THERE is a group of rare and interesting tumors of the uterus, containing a mixture of tissues of mesodermal origin, which is of especial interest to obstetricians, gynecologists, and pathologists. Various names have been applied to the group, most of them with good reason, but we have continued the use of "mixed mesodermal tumor" and "carcinosarcoma" because these names are well established in the literature and generally accepted.[1, 2]

A mixed mesodermal tumor of the uterus is a tumor of monodermal origin which contains a mixture of mesodermal elements. This mixture of cell types most frequently involves smooth muscle, striated muscle, epithelium, and cartilage, but fat, fibrous tissue, myxomatous tissue, and osseous tissue have also been reported. In most of the tumors one element of mesoderm is a sarcoma, and, when present, the epithelial mesodermal element usually is a carcinoma. Thus, it is possible to have in the same mixed mesodermal tumor combinations of sarcoma and carcinoma. When such tumors do not represent a collision between a separate carcinoma and sarcoma and are not true teratomas or "combination tumors" of multidermal origin, they are properly called carcinosarcomas. A carcinosarcoma may also contain a further mixture of mesodermal elements, chiefly cartilage.

"Confusion and controversy" seems to be the theme of most discussions of these tumors. There is confusion concerning their origin. It has been suggested that they are derived from metaplasia of uterine connective tissue,[3] from cell rests which remain after descent of the Müllerian duct,[4] from small portions of myotome carried down with the Wolffian duct,[5] from striated muscle fibers which very rarely are found in normal uteri,[6] or that they simply result from dysontogenetic growth.[7] Controversy prevails as to precisely what constitutes a mixed mesodermal tumor and therefore there is disagreement over the number of reported tumors which are acceptable as being in this category. The inability of earlier pathologists to differentiate true carcinosarcomas from carcinomas with an admixture of pleomorphic sarcomatoid cancer cells often led them to make diagnoses which would not be acceptable today. The requirement that rhabdomyoblasts be present for diagnosis is questioned by some pathologists. The terminology is confused and controversial. Although mixed mesodermal tumor is the acceptable present-day name there is no agreement that this is the best name for the group.

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Mesenchymoma, mesenchymal sarcoma, malignant mesenchymoma, combined mesenchymal sarcoma and carcinoma, dysentogenetic tumor, and many other names have been and are used.[8]

It seems reasonable that the addition of isolated case reports of these rare tumors to the brief but growing literature will add to our knowledge of the group as a whole. The chief purpose of presenting this small group of six cases, however, is to indicate again the considerable variation in pattern which the microscopic appearance may present and to show how these apparently different tumors may be fitted into the general scheme of uterine tumors under one name.

Case Reports

CASE 1.—This 50-year-old white married woman, gravida xi, para x, was admitted Dec. 21, 1951, for investigation of profuse and prolonged uterine bleeding of 12 months' duration. Cervical polyps were removed by the referring physician at a local hospital in May, 1951, August, 1951, and December, 1951. Pathology reports on these tissues were all returned as benign cervical polyps, no suggestion of malignancy. In August, after the second removal of polyps, she received approximately 1,200 mg. hr. of intrauterine radium.

Examination: Her weight was 207 pounds, blood pressure 150/90. The external genitals were normal, the vagina smooth. The cervix was distended by several large fingerlike projections of tissue which measured approximately 2 by 2 by 5 cm., which appeared to arise in the endocervix, and which dilated the cervix 3 to 4 cm. Several pieces of tissue were removed for biopsy. The uterus measured 15 by 10 by 8 cm., was irregular, firm, and freely movable, and had the consistency of a large myoma. Chest x-ray was negative.

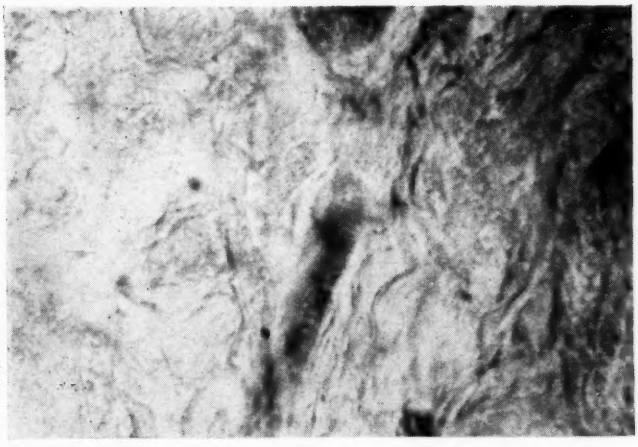

Fig. 1 (Case 1).—Mixed mesodermal tumor: Rhabdomyosarcoma with cartilage. An elongated "strap" cell with distinct cross striations. (Phosphotungstic acid hematoxylin. ×1,350. Reduced one-fourth.)

Operation: Two-stage procedure at one sitting. From below, the vagina was divided in its middle segment, freed from the paravaginal tissues. The anterior and posterior parts of the cuff were sewed together to form a pouch over the projecting masses. Abdominal approach was through a Cherney incision, and total abdominal hysteromyomectomy and bilateral salpingo-oophorectomy with removal of the vaginal pouch were done. The pouch was entered inadvertently, tumor material spilling into the peritoneal cavity. No peritoneal metastases were noted at the time of operation.

On February 22, pelvic examination was negative, chest x-ray negative. On April 22, there was a pelvic mass 10 cm. in diameter which was biopsied, with the report "mixed mesodermal tumor of the uterus." A chest film was negative. X-ray therapy was given, 13,600 r in air to six ports. On June 5, an increase in the size of the pelvic mass was noted. The patient died at home in October, 1952.

Fig. 2.

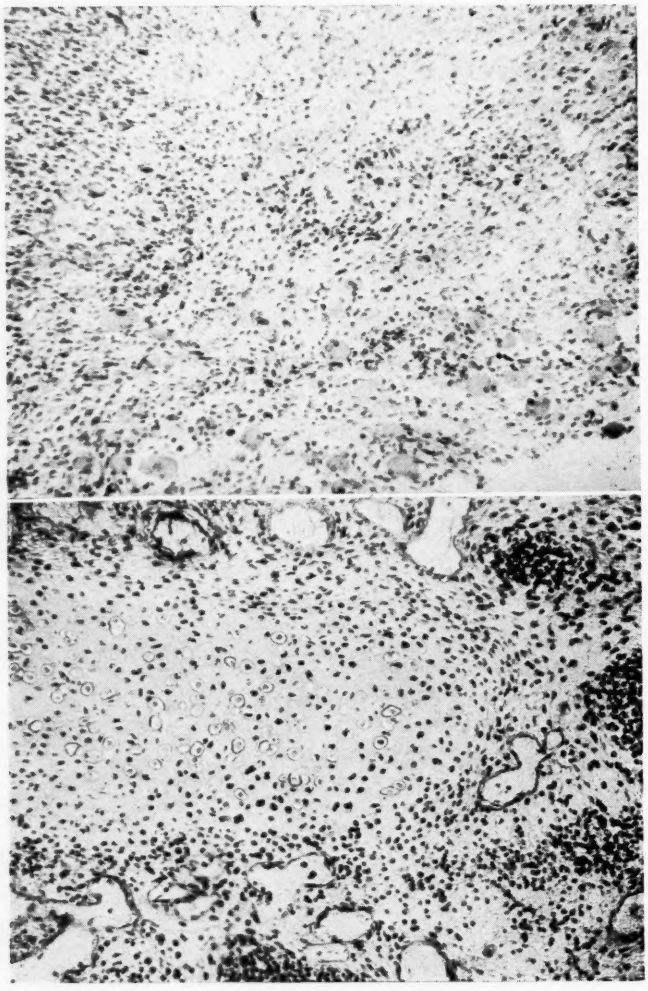

Fig. 3.

Fig. 2 (Case 1).—Rhabdomyosarcoma showing giant cells. (Hematoxylin and eosin. ×140. Reduced one-fourth.)

Fig. 3 (Case 1).—Area of cartilage in rhabdomyosarcoma. (Masson trichrome. ×140. Reduced one-fourth.)

Pathological examinations: Tissue: Endocervical polyp. Gross: Three polypoid portions of tissue, 1.5 cm. in the greatest dimension. Microscopic: All three fragments were composed of a loose pleomorphic sarcoma partially covered by columnar and stratified epithelium. There were large areas of necrosis. Small islands of atypical cartilage appeared to be formed from the sarcomatous stroma. No cross striations were demonstrated. No carcinomatous element was present.

Diagnosis: Mixed mesodermal tumor (undifferentiated sarcoma with cartilage.)

Tissue: Uterus, cervix, both tubes, and ovaries. Gross: The specimen was a previously opened 17 by 10 by 8 cm. formalin-fixed uterus, cervix, tubes, and ovaries. A large brown-to-gray, friable, necrotic tumor protruded from the cervical os in several fingerlike masses up to 6.5 cm. in length. This was attached to the cervix and endocervix. The base had a compact grayish appearance and extended onto the wall of the vagina at 8 o'clock. The tumor was infiltrative, nonencapsulated, but did not grossly extend to the parametria. In the fundus, the myometrium and endometrial cavity were distorted by a 6.5 by 6.5 by 7 cm. hard, rubbery, circumscribed, gray-white tumor of interlacing bundles and whorls of tissue. Microscopic: The tumor was composed entirely of a pleomorphic sarcoma without carcinomatous elements. No cartilage was found. There were many areas where large rounded cells with pink finely granular cytoplasm resembled muscle cells. The tumor extended onto the vagina a short distance; however, all margins were clear. Phosphotungstic acid hematoxylin stains readily demonstrated cross striations. The endometrium was proliferative but with slight dysplasia. The large fundal tumor was a benign leiomyoma and entirely separate from the cervical tumor.

Diagnosis: Mixed mesodermal tumor (rhabdomyosarcoma with cartilage). Leiomyoma.

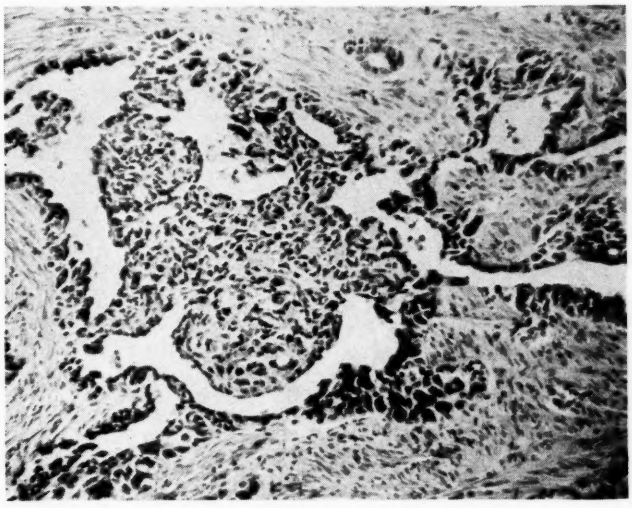

Fig. 4 (Case 2).—Mixed mesodermal tumor: Carcinosarcoma (rhabdomyosarcoma and adenocarcinoma, with cartilage). Area of adenocarcinoma surrounded by rhabdomyosarcoma (not shown). (Hematoxylin and eosin. ×140. Reduced one-fourth.)

CASE 2.—This 67-year-old white married woman was admitted to the Rockingham Memorial Hospital, Harrisonburg, Va., in January, 1950, because of profuse and prolonged postmenopausal bleeding. All of her treatment was carried out in that hospital. Physical examination showed only diffuse obesity. Pelvic examination: The external genitals and vagina were normal. The cervix was normal. There was an irregular uterine mass midway to the umbilicus, firm and nontender. The adnexa were normal. Dilatation and curettage were done. On Feb. 25, 1950, total abdominal hysterectomy, bilateral salpingo-oophorectomy and appendectomy were performed after deep x-ray therapy, 3,000 r. There was a vaginal recurrence in July, 1950. This was treated with local radium implantation. The patient died in November, 1950.

Pathological examinations: Tissue: Endometrium from the curettage. Gross: There were a moderate number of irregular, friable, light yellowish-tan bits of tissue. Microscopic: The fragments of tissue were composed of pleomorphic sarcoma. Small islands of atypical cartilage appeared to be formed from the sarcomatous stroma. No definite carcinoma is demonstrated. Phosphotungstic acid hematoxylin studies showed the presence of cross striations.

Diagnosis: Mixed mesodermal tumor (rhabdomyosarcoma with cartilage).

Tissue: Uterus, tubes, ovaries, cysts from omentum. Gross: The specimen was a formalin-fixed uterus and cervix opened along one lateral margin and measuring 8 by 6 by 4 cm. The endometrial cavity was filled by a white to brownish-black, hard to soft, pedunculated tumor which had a broad base occupying the posterior wall of the endometrial cavity and presenting at the external cervical os. Grossly there appeared to be no significant degree of invasion of the myometrium. Microscopic: The tumor was composed of both sarcomatous and carcinomatous elements. The former occurred predominately in the free end of the mass at the cervical os. It was in these areas that phosphotungstic acid hematoxylin stains demonstrated cross striations. Proximally, the tumor was largely composed of papillary adenocarcinoma which appeared to arise from the atrophic endometrium. The margins examined were of tumor.

Diagnosis: Mixed mesodermal tumor (adenocarcinoma and rhabdomyosarcoma, with cartilage).

CASE 3.—This 51-year-old Negro married woman, gravida 0, was admitted on Sept. 23, 1948, because of lower abdominal pain and uterine bleeding of five months' duration. Physical examination: There was a nodular mass filling the entire lower abdomen. One right inguinal lymph node measured 3 cm. in diameter. Pelvic: The external genitals and vagina were normal. The cervix was firm and fixed. The uterus was irregularly enlarged to the umbilicus, firm, nodular, partially fixed. A large firm, fixed, tender mass on the left extended into the left flank, inseparable from the uterine mass. X-ray of the chest and bony pelvis was negative. On Sept. 25, 1948, excision of right inguinal node was done. On Sept. 29, 1948, a supracervical hysteromyomectomy and bilateral salpingo-oophorectomy were performed. On Oct. 5, 1948, x-ray therapy, a total of 3,000 r in air, was discontinued because of reappearance of a painful pelvic mass. On Nov. 18, 1948, the pelvis was frozen. The patient died at home Dec. 6, 1948.

Pathological examination: Tissue: Right inguinal lymph node. Gross: A globular encapsulated mass of tissue measuring 5 by 2 by 1.5 cm. was soft but resilient, the surface mottled yellow to grayish-brown. The cut surface presented smooth lobules interspersed with reddish-brown areas. Microscopic: The tissue appeared to represent a lymph node in which very little of the original structure remained. There was replacement by anaplastic tumor, the cells of which were closely packed with eosinophilic cytoplasm. In some areas a tendency to papillary growth was present. Large areas of necrosis were irregularly interspersed throughout the tissue. A moderate number of mitoses was present. No striations were found on phosphotungstic acid hematoxylin stain.

Diagnosis: Metastatic anaplastic adenocarcinoma.

Tissue: Uterus, tubes and ovaries. Gross: The uterus measured 15 by 22 by 11 cm., the serosa smooth and intact. There was bulging of the serosa by several soft to firm light-tan tumors and on either side were pedunculated 10 by 7 cm. tumors, all sharply demarcated and circumscribed, composed of interlacing tan-white bundles. No cervical tissue was grossly identifiable. Throughout the myometrium there were many circumscribed tumor masses with a whorled appearance, some with calcification, others with necrosis. Projecting into the endometrial cavity were several pedunculated soft yellow-white masses. One ovary measured 6 by 3.5 by 2 cm. The second ovary measured 13 by 9 by 7 cm. and both had several soft nodular masses which were composed of white tissue with irregular brown mottling. There was considerable necrosis. Microscopic: The tumor presented a very marked degree of variation in histological appearance. The endometrium was for the most part atrophic but presented an extreme degree of atypical change adjacent to the pedunculated tumor. This histologically was compatible with an adenocarcinoma of the endometrium and extended along the surface of the pedunculated tumor a short distance. The pedunculated tumor presented a rather definite rhabdomyosarcomatous appearance in its major portion. Although this tumor was pedunculated, it invaded the myometrium where vessel invasion was present. The tumors of the myometrium as seen in the gross were benign leiomyomas showing hyaline and calcific changes. Both ovaries showed metastatic tumor which was the same as the metastatic

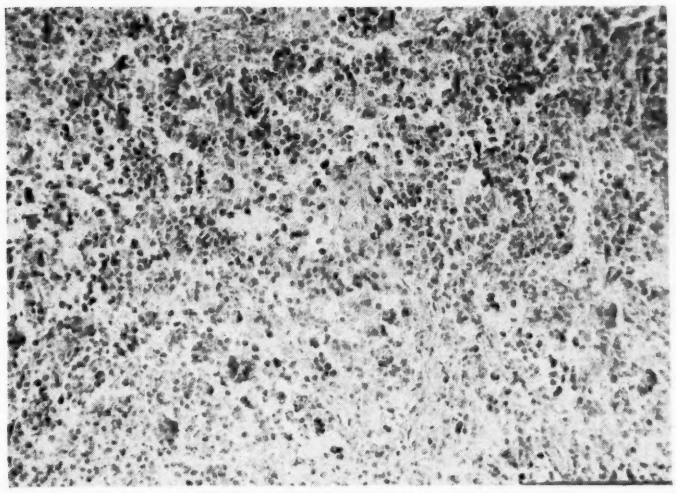

Fig. 5 (Case 3).—Mixed mesodermal tumor: Carcinosarcoma (rhabdomyosarcoma and adenocarcinoma, without cartilage). Area showing sarcoma. (Hematoxylin and eosin. ×140. Reduced one-fourth.)

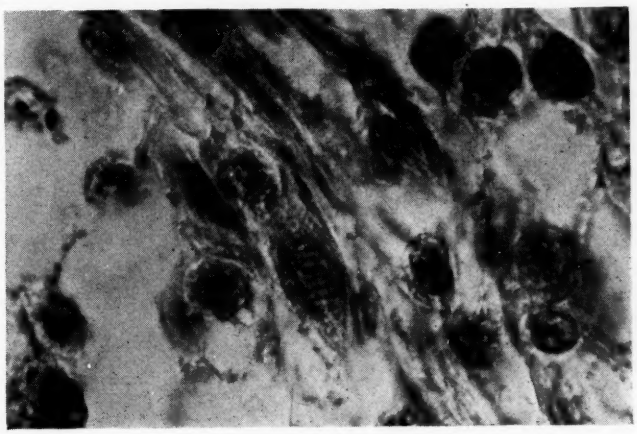

Fig. 6 (Case 3).—Tumor cell with distinct cross striations. (Phosphotungstic acid hematoxylin. ×1,350. Reduced one-fourth.)

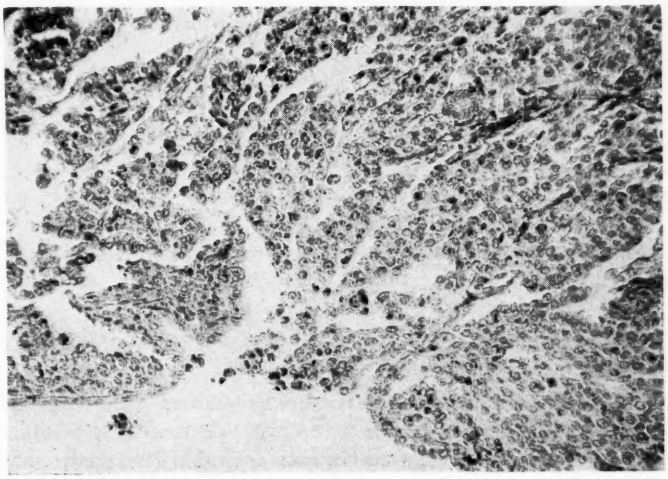

Fig. 7 (Case 3).—Area of adenocarcinoma. (Masson trichrome. ×140. Reduced one-fourth.)

tumor from the inguinal region described above but no spindle or "strap" cells could be identified. Phosphotungstic acid hematoxylin stains readily demonstrated cross striations, most easily found in the "strap" cells of the tumor of the uterus.

Diagnosis: Mixed mesodermal tumor. Carcinosarcoma (adenocarcinoma and rhabdomyosarcoma, without cartilage). Leiomyoma.

CASE 4.—This 60-year-old Negro married woman, gravida vi, para iii, was admitted on Dec. 7, 1949, because of postmenopausal bleeding of four months' duration. Physical examination: The blood pressure was 174/94. There were no palpable lymph nodes. Abdomen: There was a large, firm, nontender, fixed mass, filling the entire abdominal cavity. Pelvic: The external genitals and vagina were normal. The cervix was smooth and, pushed up high behind the symphysis, there was a large fixed tumor mass, cystic, but containing very firm areas, palpable throughout the abdomen, filling the pelvis and extending down into the rectovaginal septum. Chest film was normal. Intravenous pyelogram showed bilateral hydronephrosis. On Dec. 19, 1949, a supracervical hysterectomy and bilateral salpingo-oophorectomy were done. Much tumor tissue was left. On Dec. 29, 1949, x-ray therapy was given, a depth dose of 5,280 r to each side of the pelvis. On Feb. 25, 1950, there were no masses on pelvic examination. On March 28, 1950, chest x-ray showed metastatic lesions and fluid. The patient died April 23, 1950, at home.

Fig. 8 (Case 4).—Endometrial cavity filled with a pedunculated soft yellow-white tumor mass. The area of attachment is located in the posterior inferior surface and measures 5 cm. in diameter. Mixed mesodermal tumor: Carcinosarcoma (undifferentiated sarcoma and adenocarcinoma without other elements). Leiomyoma.

Pathological examinations: Tissue: Uterus, tubes, and ovaries. Gross: A supracervically amputated uterus with attached tubes and ovaries, measuring 18 by 17 by 15 cm. The endometrial cavity was greatly enlarged and filled with a pedunculated soft yellowish-white to hemorrhagic tumor. The base was 5 to 6 cm. in diameter and was on the right lateral and posterior wall in about the mid-portion. There were numerous similar masses of friable material from the pelvis. Microscopic: An anaplastic pleomorphic tumor, composed of intimately mingled adenocarcinoma and spindle-cell sarcoma which invaded the myometrium, had metastasized to the pelvic peritoneum as a mixture of both elements and to the left ovary as an adenocarcinoma.

Diagnosis: Mixed mesodermal tumor. Carcinosarcoma (adenocarcinoma and undifferentiated sarcoma without cartilage). Leiomyoma.

CASE 5.—This 65-year-old Negro married woman was admitted on Nov. 26, 1950, because of uterine bleeding of 12 months' duration. Pelvic examination: The external genitals and vagina were normal. The cervix was normal. The uterus was of normal size,

firm, slightly irregular, in mid-position, partially fixed. The tubes and ovaries were normal. Chest film was normal. On Nov. 27, 1950, curettage and biopsy of the cervix and endocervix were done. On Dec. 6, 1950, a total abdominal hysteromyomectomy and bilateral salpingo-oophorectomy were performed. Follow-up: Pelvic examinations were repeatedly negative. At the last examination, Jan. 22, 1953, the chest film was negative. Pelvic, abdominal, and peripheral nodes were negative.

Pathological examination: Tissue: Uterus, tubes and ovaries. Gross: Uterus with left tube and ovary attached. Removed by total hysterectomy, the uterus measured 10 by 5.5 by 4 cm. The serosa was reddish-tan and smooth except for 2 pedunculated subserous myomas on the posterior surface, one measuring 3 by 2 by 1.5 cm., the other measuring about 5 mm. There was also a third measuring about 2 mm. The consistency of the fundic portion was quite rubbery and cystic. On section of the uterus the endometrial cavity was dilated to about 1.5 cm. and filled with a polypoid structure which was attached to the fundic portion of the uterus and measured about 1.5 cm. in diameter. This tissue was light tan to orange color and variably firm and semisolid. There was no obvious gross extension into the interstitial portion of the tube. The left tube measured 6 by 0.5 cm. with the fimbriae nonidentifiable but apparently attached to the left ovary. The distal portion of the tube was dilated containing watery material. The ovary measured 2.5 by 2 by 1 cm.; the serosal surface was yellowish and wrinkled in appearance. There was a small fragment of light tan polypoid tissue present in the lumen of the tube.

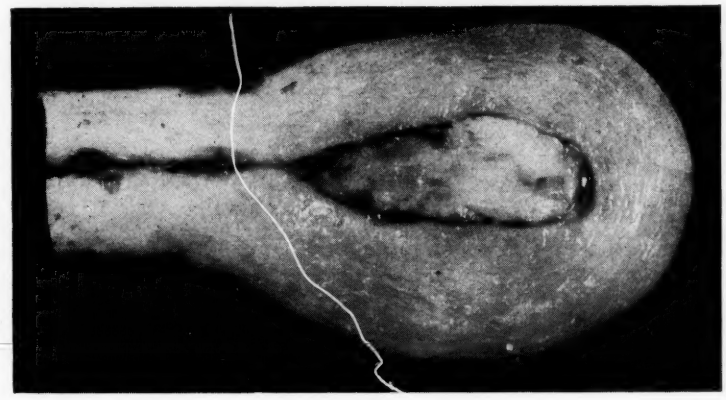

Fig. 9 (Case 5).—Endometrial polypoid mass attached high in the fundus over an area measuring 1.5 cm. in diameter. Mixed mesodermal tumor: Carcinosarcoma (undifferentiated sarcoma and adenocarcinoma, with cartilage).

The other ovary measured 2 by 2 by 1 cm. with wrinkled, yellowish-tan serosa. The consistency was firm. The tube measured 7 by 0.6 cm. with a reddish-blue smooth serosa. The lumen was patent. The cervix measured 3 by 2.5 cm., surrounding a transversely lacerated os which had previously been biopsied. Microscopic examination of the endometrium showed the fibroid tissue described in gross to be neoplastic tissue of unusual appearance, being composed in part of sarcomatous areas with the majority of the tissue being more glandular in character with large hyperchromatic columnar epithelial cells with large hyperchromatic nuclei and scattered mitotic figures. There was some rather well-defined cartilaginous material. The tumor infiltrated into the endometrium which appeared atrophic with some cystic changes. There was no evidence of invasion of the myometrium. There was marked infiltration of chronic inflammatory cells throughout the myometrium. There were two areas from the serosal surface in which there was proliferation of the connective tissue and smooth muscle in a characteristic whorllike pattern with one such area being adjacent to the myometrium. In the cervix the stroma was infiltrated with chronic inflammatory cells and there was some re-epidermization activity of the squamous epithelium with some proliferation of the squamous epithelium.

In the tubes there was some fibrosis and scarring with infiltration of chronic inflammatory cells. The material which was present in the left tube was interpreted as being proliferated tubal epithelium. There was no evidence of malignancy. The ovaries showed fibrosis and scarring with some atrophy. There was no evidence of malignancy.

Diagnosis: Mixed mesodermal tumor. Carcinosarcoma (undifferentiated sarcoma and adenocarcinoma with cartilage). Leiomyoma. (Pathological sections were submitted to Dr. Emil Novak and Dr. Robert Faulkner, both of whom returned a diagnosis of mixed mesodermal tumor.)

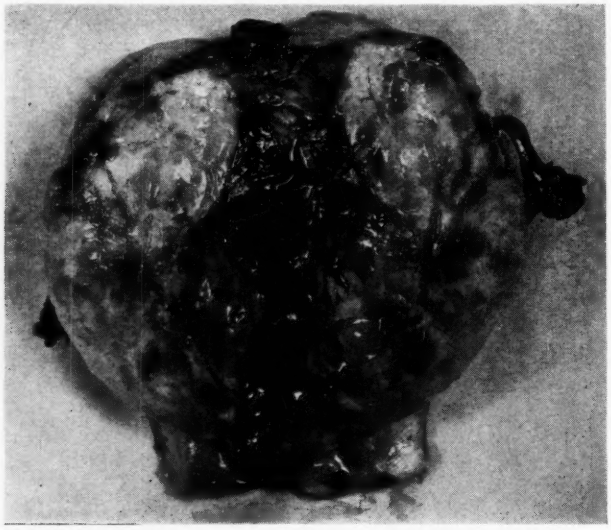

Fig. 10 (Case 6).—Large sessile fungating tumor diffusely extending into myometrium. Mixed mesodermal tumor: Carcinosarcoma (undifferentiated sarcoma and adenocarcinoma). Cartilage found at autopsy in pelvic metastases.

CASE 6.—This 72-year-old white married woman, gravida ii, para ii, was admitted because of postmenopausal bleeding of six months' duration. One year before admission she had had a radical mastectomy for carcinoma of the right breast and axillary area. Physical examination: The blood pressure was 190/110. There was no evidence of local recurrence in the mastectomy or axillary area. Pelvic examination showed normal external genitals and vagina. The cervix was normal. The uterus was in third-degree retroversion, soft, symmetrically enlarged to the size of a 3 months' pregnancy, and moderately tender. Chest film was negative. On July 27, 1951, curettage and biopsy of the cervix and endocervix were done. On Sept. 29, 1951, total abdominal hysterectomy, bilateral salpingo-oophorectomy, and appendectomy were performed. On Oct. 29, 1951, deep x-ray therapy was given, a depth dose of 4,375 r to each side of the pelvis. In January, 1952, there was no evidence of recurrence, and the chest film was negative. In March, 1952, there was no evidence of recurrence and the chest film was negative. In October, 1952, pulmonary metastases and hydrothorax were noted, with recurrence of the pelvic mass. The patient died Jan. 8, 1953. Autopsy was obtained.

Pathological examinations: Tissue: Uterus and appendix. Gross: The specimen was composed of a formalin-fixed 13 by 10 by 6 cm. opened uterus, cervix, tubes, and ovaries. The endometrial cavity contained a fungating mass of grayish-red, friable, 3 by 4 cm. tumor extending into the myometrium but not the serosa. Microscopic: The tumor of the uterus was principally composed of a spindle-cell sarcoma with poorly formed large bundles of cells that ran in different planes. No cross striations were demonstrated by phosphotungstic acid hematoxylin stain. Blending with this tumor were groups of atypical epithelial cells, some forming glandlike structures, others pseudopearls. All margins examined were free of tumor.

Diagnosis: Mixed mesodermal tumor. Carcinosarcoma (adenocarcinoma and undifferentiated sarcoma, without cartilage).

Autopsy: Pertinent findings: There was a 10 by 15 cm. local pelvic recurrence. There were numerous peritoneal implants 0.5 to 4 cm. in diameter. No gross metastases occurred in the regional lymph nodes. There were multiple parietal pleural metastases 0.5 to 1 cm. in diameter. The base of the left lung was the site of a 10 cm. metastasis which involved the diaphragm and lower portion of the left lower lobe. The base of the right lung was the site of a similar metastasis which involved the diaphragm and also invaded the bronchus of the left lower lobe. Microscopic: The recurrent tumor of the pelvis was composed of anaplastic pleomorphic adenocarcinoma with many areas of atypical cartilage formation. The parietal pleural metastases were composed of spindle-cell sarcoma arranged in interlacing bundles. The two pulmonary metastases were composed of sarcomatous elements arranged in loose bundles with a more rounded cell type. Phosphotungstic acid hematoxylin stains failed to demonstrate cross striations in the recurrent pelvic mass or in the metastases. Carcinoma was present in at least one of the peritoneal implants.

Clinical Considerations

This history of these tumors and reviews of the literature concerning them have recently been reported[9, 10] and need no further repetition. The clinical features also have been repeatedly recorded.[9, 10] Abnormal uterine bleeding without specific pattern is a clinical observation common to practically all patients. In general, tumors of the cervix have been found most frequently in girls and young women whereas tumors of the corpus are usually present in older women, especially after the menopause. Bleeding in the former group, therefore, occurs before the menarche or between menses and in the latter group after the menopause. There are numerous exceptions to these generalizations. Other unusual symptoms include passage of necrotic tissue and presentation of polyps at the introitus.

The onset of mixed mesodermal tumor after irradiation of apparently normal uteri has been frequently noted and irradiation has been suggested as an etiological factor.[8] Treatment of abnormal bleeding in benign uteri by x-ray and radium, however, has in the past been so commonplace that it would be difficult to determine from our present knowledge whether the frequent occurrence of these tumors in irradiated uteri is statistically significant. This is, nevertheless, an interesting observation and the results of an intense search in previously irradiated normal uteri for abnormal mesodermal structures would be interesting. The appearance of mixed mesodermal tumor five months after radium treatment for benign polyp is noted in Case 1. The pathological sections were reviewed by the pathologist who made the original diagnosis of benign polyp and confirmed by him.

Treatment of these tumors by x-ray seems useless since, on occasion, growth appears to be stimulated rather than retarded. Complete removal of the uterus, tubes, and ovaries has offered only palliation. It is unusual for patients to live longer than one to two years after treatment; no patient with a five-year survival has been reported. All of our patients are dead except No. 5 who, 25 months after operative treatment, without radiation, shows no evidence of recurrence.

Pathological Considerations

In infants, tumors of the vagina having similar pathologic characteristics have been reported[11, 12] but are extremely rare. In these, the exact site of origin would be difficult to prove.

Tumors of the cervix usually present a distinctive grapelike appearance (sarcoma botryoides). They may be polypoid as noted in Case 1.

Tumors of the corpus are generally present as a mass of polypoid, gray-red, smooth, friable tissue, either pedunculated or sessile. They usually invade the myometrium but seldom the serosa. The tumors may be single or multiple, large, filling and expanding the cavity of the uterus, or small, grossly resembling an innocuous endometrial polyp. Metastasis is principally by way of the blood stream but local infiltration and lymphatic spread occur frequently. It is unusual to find myomas in association with these tumors and the presence of myomas in four of our six cases is noted.

Discussion

In considering these tumors it should be recalled that except for nerve tissue, the embryological origin of all of the structures of the uterus, epithelium, glands, stroma, connective tissue, and muscle, is mesodermal.[13] It is logical to assume, therefore, that all tumors of the uterus and cervix excepting teratomas are of mesodermal origin and can be classified as mesodermal tumors.[14] This is not unusual when one reflects upon the embryology of the adrenals and kidneys and recalls that both are of mesodermal origin but produce epithelial tumors. The Wilms tumor, in fact, contains elements in common with the present series of tumors.

MESODERMAL TUMORS OF THE UTERUS

1. Carcinoma: epidermoid or adenocarcinoma.
2. Sarcoma: rhabdomyosarcoma, leiomyosarcoma, undifferentiated.
3. Mixed mesodermal tumor.
   - A. Carcinosarcoma: rhabdomyosarcoma with carcinoma.
     1. With other mesodermal elements.
     2. Without other mesodermal elements.
   - B. Carcinosarcoma: leiomyosarcoma with carcinoma.
     1. With other mesodermal elements.
     2. Without other mesodermal elements.
   - C. Carcinosarcoma: undifferentiated sarcoma with carcinoma.
     1. With other mesodermal elements.
     2. Without other mesodermal elements.
   - D. Rhabdomyosarcoma with other mesodermal elements.
   - E. Leiomyosarcoma with other mesodermal elements.
   - F. Undifferentiated sarcoma with other mesodermal elements.
4. Benign neoplasms.

We are reluctant to burden the literature with another classification, already too numerous, of these tumors. The foregoing one is set down simply to show how tumors of different cell pattern may be grouped under the name "mixed mesodermal tumor" and how this group of tumors fits into the general scheme of mesodermal uterine neoplasms.

The patients presented here may be fitted into various categories of this classification. Case 1 represents the subgroup, "rhabdomyosarcoma with other elements." Case 2 represents the subgroup "rhabdomyosarcoma and adenocarcinoma with other elements." In this case, cross striations were demonstrated as well as carcinoma and cartilage. Case 3 represents the same subgroup but without cartilage. Only these three patients would be acceptable to those pathologists who require the demonstration of rhabdomyoblasts for the diagnosis of mixed mesodermal tumor. Case 4 represents the subgroup "undifferentiated sarcoma and adenocarcinoma without other elements." Phosphotungstic acid hematoxylin stains were not done on the original tissue and no other tissue was available for further staining. Case 5 represents the subgroup "undifferentiated sarcoma and adenocarcinoma with other elements." Case 6 falls into the subgroup "undifferentiated sarcoma and carcinoma without other elements." The finding at autopsy of separate carcinoma and sarcoma makes it unlikely that the sarcoma element was pleomorphic carcinoma. Cartilage was present in the pelvic metastasis. The diagnosis of mixed mesodermal tumor was made on another patient in whom combined epidermoid carcinoma and sarcoma were present in the same cervical and uterine lesions. This patient was excluded because the location and appearance of the lesion and the clinical course strongly suggested the possibility of a collision between a separate carcinoma and sarcoma. Two patients with sarcoma botryoides have been previously reported from the Department of Obstetrics and Gynecology.[15] Cases 3 and 4 were included in the same report but were not discussed in detail.

Although the clinical picture as well as the gross appearance of mixed mesodermal tumors of the cervix and of the corpus is more or less uniform for each location, the microscopic appearance of the tumors may vary considerably in different patients regardless of the location of the tumor. Thus, the microscopic appearance of a mixed mesodermal tumor of the cervix, having the typical gross grapelike form of sarcoma botryoides in a child, may be similar to a large sessile mixed tumor of the corpus in a postmenopausal patient. On the other hand, two mixed tumors of the corpus having similar clinical and gross pathologic features may have different cell patterns.

These differences of microscopic appearance have caused much controversy concerning which tumors are acceptable as mixed mesodermal tumors. Opinions have varied from acceptance of none to a fairly liberal acceptance of mixed mesodermal tumors as noted in the present classification.

Dispute will certainly continue until the question of exact histogenesis, now very speculative, is settled. For instance, there will be criticism for including leiomyosarcoma and undifferentiated sarcoma, with other mesodermal elements, in the present classification, as mixed mesodermal tumors. The objection will be that these are simple mesodermal sarcomas, parts of which have undergone cartilaginous metaplasia. We agree that this is very possibly so. One can, however, carry the argument of metaplasia through all of the types of mixed mesodermal tumor and conclude that there is no such tumor, that any of the types listed simply represents a combination of malignant and benign metaplastic elements of the original tumor. Others will

disagree with this extreme view and point out that although metaplasia may account for some of the combinations, it will not explain the occasional presence of rhabdomyosarcoma which develops from peripheral rather than visceral mesoderm and should, therefore, be foreign to the uterus. In rebuttal to this one recalls the frequent derivation of striated muscle from visceral mesoderm in other parts of the body (esophagus, face) and in lower animals (lower end of esophagus in dog). Our contention is that at present we do not know how the tumors are developed, or why their content should differ one from the other. Therefore, we have included, for the present, any tumor which contains combinations of mesodermal tissue.

When new methods of study enable us to isolate and identify a given tumor, and trace its origin, we will not only be able to name the tumor precisely but a more exact description of the clinical course of the tumor will follow. Present methods of diagnosis are constantly being altered, as are attempts to facillitate morphological and clinical correlations. When methods are found further to isolate cell types in these tumors we will have a better understanding of the group.

The restricted viewpoint of including only tumors showing embryonal myoblasts combined with heterologous elements such as cartilage, etc., has not been generally accepted. The presence of eosinophilic granules as an aid in the identification of rhabdomyoblasts has recently been re-emphasized.[8] Other combinations of mesodermal tumors, as noted in the present classification, may present similar clinical and gross pathologic appearances and it does not seem wise to exclude any particular group with our present limited knowledge of their origin. Exception to this, of course, as previously stated, is the blending of two separate malignant tumors, each of which should be considered as a distinct neoplasm,[1] and tumors of multidermal origin.

Summary

Six patients with mixed mesodermal tumor of the uterus are presented. The microscopic appearance of these tumors is not constant but varies without regard to location of tumor. Distinct cross striations in muscle cells are demonstrated in only three of the six tumors.

Arguments for inclusion of all of such tumors in the group of mixed mesodermal tumors are repeated and a classification is added to show how tumors of varying cell patterns, containing a mixture of mesodermal elements, may be included under the general name "mixed mesodermal tumor."

We wish to thank Dr. James R. Cash, Chairman of the Department of Pathology, for reviewing the microscopic sections, and Dr. Paul S. Hill, Harrisonburg, Va., for supplying the history in Case 2.

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Discussion

DR. R. GORDON DOUGLAS, New York City.—Dr. Wilson and his associates are to be congratulated on presenting this most interesting material for our consideration. They have reported 6 cases all of which were seen in their clinic in recent years. In fact, all of these patients were apparently encountered since 1948 which undoubtedly means that this rare tumor must occur very much more frequently than has been indicated in the literature. As recently as February, 1952, Hardy and Moragues reported two cases and reviewed the literature in great detail. They concluded that only 95 authenticated instances of this disease had been reported prior to 1941. In the intervening years between that date and 1950 they found 19 other cases reported, making a total of 116 such tumors that were described up to that time. Contrary to this interpretation of the described material in the literature, Amolsch (Professor of Pathology at Wayne University Medical College) in 1939 reported 6 cases and concluded that there were 447 instances reported at that time. This difference in the reported incidence exists to some extent because of different diagnostic criteria employed by pathologists.

In view of this great discrepancy in the literature and the relative frequency with which the essayist has found this disease in his institution, I made some inquiry in several different areas of the United States in an attempt to gather additional information concerning the actual frequency of occurrence. Rutledge in Houston, Texas, has had 2 typical instances of this disease that occurred during the past year in the M. D. Anderson Hospital. Pierce and Foote in an incomplete survey of their material at the Memorial Hospital have been able to uncover a dozen cases that have been seen during the last few years and undoubtedly these cases all represent typical mixed mesodermal cell tumors. Hertig and his associates in Boston have uncovered 11 cases in their laboratory that have occurred in recent years. Traut, at the University of California, has half a dozen cases, including 2 typical instances of sarcoma botryoides, one in a 9-month-old infant and the other in a 14-year-old girl. Collins, and Smith from Tulane report having seen 20 cases of the Charity Hospital in New Orleans since Jan. 1, 1946. With the exception of 11 of the cases from New Orleans, reported in 1951, none of these cases have been recorded in the literature. Therefore, it appears that this disease occurs much more frequently than has hitherto been suspected.

One of the difficulties encountered in locating these cases was based on the fact that they are most frequently indexed in the laboratories and clinical records as instances of endometrial carcinoma or sarcoma and are accordingly filed with the records of patients who have carcinoma of the endometrium. In nearly 30,000 gynecological admissions in our own institution we have no instance of a mixed mesodermal-cell tumor so classified. We have seen a considerable number of patients with "carcinosarcoma." Some of these tumors may actually represent instances of the co-existence of carcinoma and sarcoma and not true mixed mesodermal-cell tumors. Undoubtedly, however, a considerable number belong in this latter category. Accordingly, it seems that in order to find the true incidence of this disease it would be necessary not only to review a large amount of pathological material but also to cut many new sections. Amolsch has reported 6 cases, all in patients who had benign-appearing large polyps when first seen. The pathological examination of the re-

moved tissue in all but one instance was reported as a benign polyp. The true nature of the disease was later recognized for the first time when widespread involvement became apparent. Such errors also tend to decrease the frequency with which this disease is reported. When single blocks from a given tumor are sectioned and studied the true nature of the lesion may be completely overlooked. Oftentimes it is only when sections from many different areas of a tumor are cut that the varied mesodermal tissues are found. In view of what has been said, it appears probable that the disease will be reported much more frequently in the years to come than it has been in the past. It is for this reason that I believe great credit should go to the present authors for calling our attention to this condition.

With respect to terminology, McFarland in 1935 was able to tabulate a list of 116 terms that have been used to designate various neoplasms which, on the basis of histogenesis and composition, might be classified as mixed mesodermal-cell tumors of the uterus. I think the authors have done well to put down a simple classification based on different cell patterns that are encountered in mixed mesodermal-cell tumors. It seems to me that for the immediate future the most important thing is early recognition of these tumors in the office, in the operating room, and in the laboratories, as mixed mesodermal-cell tumors. Subsequently, a subclassification of different tumors based on the different mesenchymal structures found along these lines will undoubtedly be necessary and it may well be that the classification proposed by the essayists will be very helpful in forming a basis for such a classification. Unless many areas in a given tumor are studied errors in classification will undoubtedly be made.

All who have studied this disease are agreed that the prognosis is extraordinarily serious. In fact there are only one or two instances reported in the literature of a patient who has survived for longer than 5 years. The essayist has reported his Case 5 who has lived for just over 2 years and is presently free of disease. Only one of the patients with such a tumor that Collins and Smith have seen is living at the present time and in that instance it is only 10 months since the original diagnosis was made. The longest survival in their cases was 27 months. An unreported patient was seen and treated at the Memorial Hospital 9 years ago and that patient is now living and well. I know of no longer survival than hers. She was 60 years of age and gave a history of 2 months' bleeding. Treatment consisted of removal of the pelvic organs without the benefit of radiation.

Most writers on this subject have indicated the polypoid nature of the lesion and Amolsch has particularly stressed the rather benign gross appearance of such polypoid structures. In fact, 5 of his 6 reported cases were treated as if they were large benign endometrial or cervical polyps. Sections taken of some of these specimens revealed benign tissue and it was only after many sections were restudied that the true nature of the primary lesion was discovered. Another similar instance was noted by Foote at Memorial Hospital. Again several sections from a polyp revealed no unusual findings while one section showed definite and varied mesenchymal elements including cartilage. It is extraordinarily difficult, from a point of view of histogenesis, to visualize how a "cell rest" could occur in the middle of a large endometrial polyp!

In studying case histories of some of the material I have collected from different sources I have been impressed with the high percentage of Negro patients afflicted as compared to white. Collins and Smith report a ratio of Negro to white gynecological admissions of 2.5:1. At the same time their mixed mesodermal-cell tumors were found 4 times more frequently in the Negro patient. At the Memorial Hospital only 2 of 12 cases occurred in Negro patients. Dr. Wilson and his associates have reported 3 Negro patients with the disease, 2 white, and one unknown. Another clinical fact that seems interesting is that a considerable number of patients had been irradiated previously for benign uterine conditions.

We are indebted to the authors for their valuable presentaton. While the prognosis in the past has been grave, practically all reported cases have been first diagnosed in the late phases of the disease. With early recognition maybe the outlook will not be so hopeless. Thank you for the privilege of discussing this interesting subject.

DR. JOHN R. KIGHT, Norfolk, Va.—Dr. Wilson and his co-workers at the University of Virginia Hospital have chosen a very timely subject, that of a tumor which apparently is not so rare as formerly thought, and one about which a great deal of confusion exists, a tumor which may some time be iatrogenic, caused by the physician who treats a patient with radiation.

Dr. Wilson's Case 1 did, for example, follow irradiation. There was, however, an interval of only 5 months between irradiation and appearance of the malignant growth. The comment might be made therefore that the mixed mesodermal tumor existed, but was not discovered, at the previous biopsies.

A study similar to Dr. Wilson's has been made at DePaul Hospital to determine the incidence of this neoplasm, and the frequency of previous irradiation. This study included a review and reclassification of the specimens sent to the Pathology Department of DePaul Hospital during a 10 year interval beginning January, 1943. In this period there has been a total of 6 mixed mesodermal tumors, 2 of which followed irradiation. The table gives a summary of these cases.

MIXED MESODERMAL TUMORS, DEPARTMENT OF PATHOLOGY, DEPAUL HOSPITAL, 1943-1952

CASE	AGE	RACE	DATE	HISTOLOGICAL ANALYSIS*			SURVIVAL	IRRADIATION
				E	R	C		
V. B.	34	C	10/43	–	–	+	Died 1/45	No
E. W.	54	C	2/48	–	–	+	Died 11/48	No
F. C.	49	W	7/49	+	+	–	Died 6/50	2,400 mg. hr.
M. B.	59	C	8/51	+	+	?	Alive	No
L. P.	49	C	4/52	?	?	+	Died 7/52	No
D. P.	57	C	10/52	+	+	+	Alive	7,590 mg. hr. 9,000 r

*E, Atypical epithelial elements.
R, Rhabdomyoblasts.
C, Cartilage.

This tumor was diagnosed in 5 patients between the ages of 49 and 59, a sixth at 34 years of age. That there is a racial factor involved is suggested by the occurrence of this tumor in 5 Negro patients, and in only one white. The essayist likewise had more Negro patients.

Histological analysis of these cases revealed the following: Three cases showed glands with malignant epithelium. These mixed mesodermal tumors were subclassified as carcinosarcoma. A fourth case showed questionable epithelial elements. Three cases showed rhabdomyoblasts, identified by acidophilic granules; one case was questionable. Unequivocal cross striation could not be found. Failure to demonstrate striation may have been a result of the routine use of formalin-fixed material and hematoxylin and eosin, which is not the ideal method of showing these structures. Four of the 6 cases showed cartilage and one a questionable island of this tissue.

Treatment consisted of surgery only. No patient received postoperative irradiation. Two cases were treated by supracervical hysterectomy; the others by total hysterectomy. That this tumor is highly malignant and not amenable to simple removal of the primary lesion and warrants a poor prognosis is evident by the survival period in this series. Of the 6, 4 died within 14 months following hysterectomy. One is alive and well 16 months after treatment and a recent case has been followed only 3 months.

Of the 2 patients who had had previous irradiation, one (F. C.) had been treated 6 years before with 2,400 mg. hr. of radium for a benign lesion, metrorrhagia. The other (D. P.) had received 7,590 mg. hr. of radium and 9,000 r for epidermoid carcinoma of the cervix in November, 1947, 5 years prior to operation. As shown, our material contains 2 cases of previous irradiation in 3 carcinosarcomas, or in 6 mixed mesodermal tumors. It is our belief that these 2 cases support the opinion that irradiation can be the carcinogenic factor in mixed mesodermal tumors.

THE PROBLEM OF THE UTERINE FIBROID*†

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THE nonpregnant, enlarged uterus, is by no means a new problem in medical practice. Fletcher Shaw,[1] many years ago, described three types of diffuse nonpregnant uterine enlargement. The first, chronic subinvolution, included 70 per cent of all diffuse enlargements of the uterus. In this type Shaw noted no increase in connective tissue. The second type of uterine enlargement was due to chronic metritis. This constituted 15 per cent of diffuse uterine enlargements. In this condition Shaw noted a marked increase in connective tissue. This latter observation has been confirmed by Otto Schwarz[1] who, in some instances, noted as much as 80 per cent connective tissue and 20 per cent myometrium. Shaw found uterine hypertrophy to be the least common cause of diffuse enlargement, constituting approximately 5 per cent of all cases. Here, again, no increase in connective tissue was noted, the enlargement being due almost entirely to an increased amount of muscle. None of the diffuse enlargements mentioned above are as common as the interesting group of localized tumors which we call fibroids. The term "fibroid" as here used includes such synonyms as myoma, fibromyoma, leiomyofibroma, etc. When taken together, uterine enlargements, both diffuse and localized, constitute one of the largest groups of cases of uterine pathology encountered by the gynecologist.

While the growth characteristics and other features of fibroids are well known, we should like to comment briefly on some of the more important ones since they have a definite bearing on the theme of this paper. It is well known, for example, that uterine fibroids are commonly isolated, encapsulated, single or multiple, benign tumors composed of muscle tissue and varying amounts of fibrous connective tissue. These tumors reach the clinical horizon and are, therefore, commonly discovered in the third and fourth decades of life but, in all probability, they began their growth very much earlier, possibly at adolescence. This early, preclinical growth of uterine fibroids preceding recognition is, we believe, an important fact to keep in mind. Fibroid tumors vary considerably in size. The largest fibroid removed by us weighed 40 pounds. The largest tumor about which we have any knowledge weighed 120 pounds and was found in a rhinoceros.

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There may be no symptoms associated with or produced by uterine fibroids. On the other hand, pressure symptoms are not infrequently mentioned. While there can be no denying that fibroids of considerable size may cause pressure it should be pointed out that this cause and effect relationship is extremely difficult to evaluate. Some women have very large uterine fibroids with no symptoms, others have relatively small tumors and report pressure symptoms. Whether this pressure is real or imagined can be determined only by careful evaluation of the tumor, its size and location, and the individual in whom it occurs.

Hypermenorrhea, or increased menstrual flow is not infrequently attributed to uterine fibroids, especially to the submucous variety. There is, of course, an interesting relationship between the occurrence of hypermenorrhea and certain submucous fibroids. On the other hand, it is also of some interest to point out that fibroids do not bleed. Except in the rare situation where hemorrhage occurs into the tumor itself, the so-called red infarction, bleeding does not come from the tumor mass. While, in some instances, the location of the fibroid beneath the endometrium causes deformity of the blood supply to the endometrium and thus, in turn, probably contributes toward an increased menstrual flow, this is not the situation in the majority of cases. In most instances of hypermenorrhea associated with uterine fibroids there exists an associated hyperplasia and irregular shedding of the endometrium which probably accounts for the excessive flow. Perhaps the exact mechanism resulting in hypermenorrhea from a uterus containing a submucous fibroid varies in different individuals. It has long been recognized that the association of endometrial hyperplasia and uterine fibroids is a common one. Both endometrial hyperplasia and hypermenorrhea also occur in the absence of uterine fibroids. Yet, there is reason to believe that the hypermenorrhea is the result of factors leading to both the endometrial hyperplasia and bleeding rather than to the fibroids per se. We shall have more to say about the cause of uterine fibroids later on but for the present it is well to contemplate a possibility which has long been recognized, namely, that uterine fibroids and hypermenorrhea probably do not represent a cause and effect relationship; rather, that the fibroid and the hyperplasia are both the by-products of a common cause.

One of the commonest symptoms of uterine fibroids may be described as "tumorophobia." This concern may be displayed by both patient and physician. With the present emphasis on the undesirability of tumors, some physicians have acquired the philosophy that any abnormal growth ocurring in the human body is better out than in. One cannot argue too much with this type of philosophy since the basic principle appears reasonably sound. However, when properly seasoned with a dash of practicality it becomes obvious that such philosophy could not logically apply to many small, completely asymptomatic fibroids. Tumorophobia may be instilled unintentionally into the minds of patients by comments voiced by the examining physician. The patient may be reassured at the time of examination that she has a small asymptomatic fibroid tumor requiring only observation. Yet, use of the word tumor slowly germi-

nates concern in the patient's mind. Over a period of months or years she learns of symptoms occasionally associated with these tumors and before long some of these, especially pressure symptoms, are acquired by the patient.

The diagnosis of uterine fibroid is generally made at the time of pelvic examination. Since many patients with uterine fibroids are completely asymptomatic, their presence frequently comes as somewhat of a surprise. Diagnosis is seldom difficult although the larger degenerating tumors may resemble ovarian cysts.

The management of uterine fibroids falls into a number of different categories, depending upon such factors as the patient's age, symptoms produced, size of the tumor, and the doctor's philosophy regarding their management. Generally, on the basis of these factors, therapy boils down to doing nothing, especially when the fibroid is small, asymptomatic, and found in a middle-aged woman approaching the menopause. As ovarian function ceases such tumors may be expected to undergo regression. If the tumor occurs in a young woman desirous of having children, or in whom, for psychologic purposes, retention of the uterus seems important, then myomectomy may be the solution. Myomectomy is not a new procedure. It is, therefore, rather surprising that myomectomy does not more often supplant hysterectomy. Enucleation of such tumors is satisfactory when carried out in properly selected cases. Victor Bonney[2] wrote a book on the subject in 1936. He also reported removing over 200 tumors from a single uterus. One might ponder upon the condition of a uterus after such extensive involvement by new growth and surgical trauma. In most candidates for myomectomy no such "berry picking" is required of the surgeon. Hysterectomy is today the most common remedy for symptomatic fibroids. When clearly indicated, it represents a satisfactory means of ridding the patient of the tumor. The use of irradiation, either x-ray or radium, in the treatment of fibroids has, we believe, decreased considerably. Certainly the majority of symptomatic fibroids are best treated surgically, but irradiation may occasionally be helpful for the control of symptoms in patients who are extremely poor surgical risks.

The high incidence of uterine fibroids is one of the characteristics which places them in the problem category. Their common occurrence is supported by the frequency with which they are encountered during routine pelvic examination, and by the fact of their being the commonest reason for hysterectomy. In a recent report by Charles Smith,[3] 60 per cent of his hysterectomies were done for uterine fibroids. Pathologists frequently mention fibroids in their evaluation of extirpated uteri, albeit many of these are small and of no significance. It has been estimated that one out of every four or five women over 35 years of age has uterine fibroids. Montgomery,[4] in a study of autopsy records at the Massachusetts General Hospital and the Johns Hopkins Hospital, found that 28 per cent, or well over one-fourth of all women over 35 years of age had uterine fibroids. Because of its common occurrence, the tumor presents diagnostic, therapeutic, psychologic, economic, and other problems. No problem, however, is more important than that which pertains to its etiology. Why do so many women develop uterine fibroids? *This, to us, is the problem of the uterine fibroid.*

Out of the sum total of medical energy expended on uterine fibroids in one way or another, little has been devoted to the basic problem of determining why fibroids exist and what makes them grow so luxuriantly.

In delving into the concepts regarding the causation of uterine fibroids one finds mention of heredity. Doubtless, heredity plays a role and helps to explain the occurrence of fibroids in a mother and daughter, in sisters, in twins, and may partially explain the high incidence in Negro women. In this latter connection, however, it is of some interest to note that medical missionaries[5] have reported an extremely low incidence of fibroids in pure African tribes untouched by so-called modern civilization. The American Negro reprerents a mixture of tribes and, furthermore, as has been reported by Matas,[5] at least one-fourth of the American Negroes have been contaminated by Aryan blood. While heredity plays an important part in the occurrence of other neoplastic diseases, it is obvious that heredity alone is not likely to account for the frequent occurence and luxuriant growth of these tumors.

The fact that fibroids make their appearance during the years of greatest ovarian activity, and tend to shrink after the menopause, has lent support to the belief that estrogen is in some way related to their development. Witherspoon[6] believed that a long-sustained elevated estrogen level provided the impetus for their growth. He explained their common occurrence in Negro women as probably due to the pelvic inflammatory disease so commonly noted in the Negro race, the inflammatory involvement of the ovaries resulting in cystic change and ovarian dysfunction which in turn led to an elevated estrogen level in the blood stream. Witherspoon reported a series of cases wherein this interrelationship appeared to exist. Much evidence has appeared in the literature supporting an underlying estrogen factor in the causation of uterine fibroids. Thus, Nelson[7] in the United States and Lipschutz[8] in South America demonstrated that it was possible to induce the formation of fibromas (not myomas) in castrated guinea pigs by the prolonged administration of estrin. Implanted estradiol pellets were a common source of estrogen in these experiments. Lipschutz encountered difficulty in attempting to produce fibromas in noncastrated guinea pigs. In a later work, he[9] attributed a tumorigenic or, to be more specific, an antiestrogenic effect to progesterone. The simultaneous administration of estrogen and progesterone to castrated guinea pigs resulted in few fibroids, quite contrary to the high incidence demonstrated when estrogen alone was used.

This antitumorigenic or antiestrogenic effect of progesterone is of considerable interest and may explain some of the peculiarities noted in the human being. Thus, it has been stated that women with fibroids have low fertility. It was once thought that because they did not bear children they developed fibroids. Today the concept is generally reversed, many physicians believing that the presence of these tumors interferes with conception. However, it is also possible that women who develop fibroids may have had during their earlier years, a high percentage of anovulatory cycles, there may have been fewer eggs produced and prolonged estrogen stimulation over a long period of time, without interruption and the countereffect of progesterone such as would normally have occurred with regular ovulatory cycles. This antagonistic effect of progesterone

upon the growth of fibroids has been clinically demonstrated by Goodman.[10] Similarily, the presence of progesterone in the blood stream during pregnancy may explain the interesting observation made by Randall and Odell[11] that, contrary to accepted opinion, fibroids do not enlarge during pregnancy. Perhaps progesterone also accounts for the quiesence of pelvic endometriosis during pregnancy.

Lipschutz noted that both desoxycorticosterone and testosterone had antitumorigenic or antiestrogenic effects when used with estrogen in an attempt to produce fibromas in castrated guinea pigs. Vargas, on the other hand, was unable to produce fibroids in castrated monkeys by means of prolonged estrogen administration. However, he did cause some diffuse uterine enlargement. While it is very difficult to induce growth of fibroids in castrated rats, Pfeiffer[12] was able to do so in rats treated with estrogen over a period of 3 years. The specific tumorigenic effect of prolonged estrogen administration in the castrated guinea pig is interesting when viewed in light of the work carried out by Engle and Smith[13] and also by Hisaw.[13] The latter found that, in the monkey, a combination of estrogen and progesterone was more growth-stimulating to the uterus than was estrogen alone. Furthermore, the localized effect of estrogen administration in the castrated guinea pig requires some contemplation. If estrogen were the only factor necessary for the production of uterine fibroids, one might expect an even higher incidence in women. It is difficult to comprehend this localized isolated response to estrogen on the part of uterine musculature, since one might logically anticipate a uniform response on the part of all identical cells. How then can one explain this isolated, encapsulated tumor which in the castrated guinea pig at least, may develop in response to prolonged estrogen administration?

Obviously, while estrogen appears to be a big factor in the development of fibroids, it cannot be the sole factor accounting for their development. When we combine heredity and the estrogen stimulation theory with still another, the cell-nest theory, the formation of these tumors becomes understandable. If we accept the existence of cell nests, which under propitious circumstances become fibroid tumors, it then becomes easy to explain the localized nature of the growth; the failure of the remainder of the uterus to participate; the fact that these tumors do not occur in all women; and the low incidence of recurrence following myomectomy. Following adequate myomectomy, less than 3 per cent of patients show recurrence. Yet, if fibroids were merely the product of estrogen stimulation alone, susceptible individuals should reveal a high incidence of recurrence. It would appear that the existing low incidence of recurrence can be explained on the basis of small "seedlings" overlooked at the time of operation rather than upon the development of entirely new tumors.

Robert Meyer[14] observed what he considered to be immature muscle cells in the uterine wall. They were 0.02 to 0.20 mm. in diameter. He suspected these might be incipient myomas. De Snoo[15] believed that the uterus contained many undifferentiated muscle cells which he called "genitoblasts." He believed that under proper conditions of ovarian dysfunction, these genitoblasts could grow into uterine fibroids, endometriomas, or adenomyomas.

It appears, then, that we have a reasonably satisfactory explanation for the occurrence of uterine fibroids in some women. Their occurrence would seem to depend on three important factors: the presence within the myometrium of small, immature muscle-cell nests, which under appropriate estrogen stimulation develop into distinct encapsulated fibroid tumors. Possibly susceptible women have a high incidence of anovulatory cycles, permitting prolonged estrogen stimulation without interruption or interference by progesterone.

With these explanations to account for the presence of uterine fibroids, we may now justly question the value of these concepts. Of what practical value is this information? Certainly there does not appear to be much we can do about the presence of cell nests in the myometrium nor about hereditary factors predisposing to fibroid-tumor formation. Granting the correctness of this assumption, is there nothing we can do about controlling actual growth and development of these cell nests? Witherspoon does not consider the cell origin important. He does believe, however, the factors responsible for their growth, such as estrogen, are important. This, indeed, is a bird of a different feather, and perhaps it is in this direction that our successors may find a solution to the control of fibroids. At any rate it appears that if it were possible to grow human myometrium in vitro much might be learned regarding factors which encourage or inhibit its growth.

A review of the literature failed to disclose evidence that human myometrium had been cultivated in tissue culture although we did find one brief report on an attempt to culture human myoma.[16] Our first problem then has been to develop a suitable technique for the growth of human myometrium and myoma in vitro. Once this has been satisfactorily accomplished it should be possible to evaluate, under controlled conditions, the factors which contribute to or inhibit the growth of myometrium and myomas.

The technique used by us has been to obtain specimens of myometrium and myoma from the same individual at the time of hysterectomy. Small explants, about 1 mm. square, were prepared for cultivation. These fragments were planted directly on the glass surface of ordinary Pyrex test tubes or on No. 1 thinness cover glasses measuring 12 by 22 mm. which had previously been inserted in the test tubes. After allowing 15 to 30 minutes for proper adhesion to occur, 1 ml. of nutrient fluid was added. This consisted of 40 per cent human placental serum, 4 per cent chick embryonic extract, and 56 per cent Hanks' balanced salt solution. Following the addition of the medium, the tubes were tightly sealed with rubber stoppers and incubated at body temperature in a roller tube apparatus[17] designed to complete 10 revolutions per hour.

For the first five to seven days the explants revealed no activity but at the end of a week or therabouts, migration of individual spindle cells of various sizes occurred. In a few days the cellular proliferation became intensified and soon a radial reticulum was formed (Fig. 1). Since these cells were quite indistinguishable from ordinary fibroblasts, identification of the proliferating cells has become an important part of our study. In aiming at positive identification we have employed diverse approaches to this basic problem. These may

be listed as follows: (1) growth characteristic studies; (2) differential staining of original sectioned tissue as compared to sections of fragments cultivated in vitro; and (3) differential staining of whole mount cover-glass cultures.

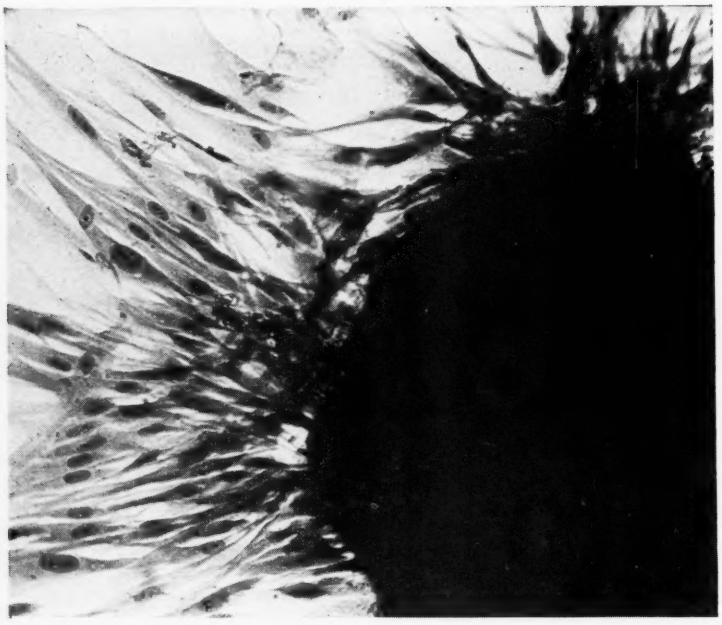

Fig. 1.—Radial reticulum of spindle-cell outgrowth from a myometrial explant after 30 days' cultivation in vitro. (Bouin's fixative. Masson trichrome stain. ×75.)

In general, growth characteristic investigations revealed that myometrium and myoma have a similar proliferative potential and pattern of development. However, if a high degree of connective tissue infiltration has occurred (fibrotic tumors), the outgrowth of tumor cells is slower and less extensive than for myometrium. Presumably, if the proliferating cells were of a connective-tissue origin, namely, fibroblasts, one would expect a faster growth rate from these fibrotic tumors.

Employing Masson's trichrome differential stain we have compared sections of original tissue with those of fragments cultivated for various periods of time in vitro. The typical picture of myometrium as seen in sections is one in which the smooth-muscle fibers are arranged in cylindrical or flat bundles and take the red stain. These red-stained muscle bundles are separated from one another by thin bands of blue-staining interstitial connective tissue containing isolated smooth-muscle cells. On the other hand, as seen in our laboratory, the appearance of myoma (fibroid) is one in which varying degrees of myofibrosis has occurred. Thus large bands of blue-staining connective-tissue stroma replace to a considerable extent the red-staining muscle cells. Consequently, the muscle bundles are smaller and fewer in number. However, after a fragment of either tissue has been grown in vitro for sufficient time to permit extensive proliferation, stained sections reveal an entirely different histological picture. Such a

fragment section presents a capsule of active red-staining cells from which the radial reticulum of proliferating cells migrate, completely enclosing a core of dense blue-staining connective tissue elements. Such a myometrial explant reproduced in black and white is shown in Fig. 2. The only observable difference between myoma and myometrial explants sectioned and stained in this manner is the presence of a slightly greater accumulation of blue-staining centrally placed connective tissue stroma in sectioned myoma fragments, an observation which is consistent with the fact that connective tissue elements are

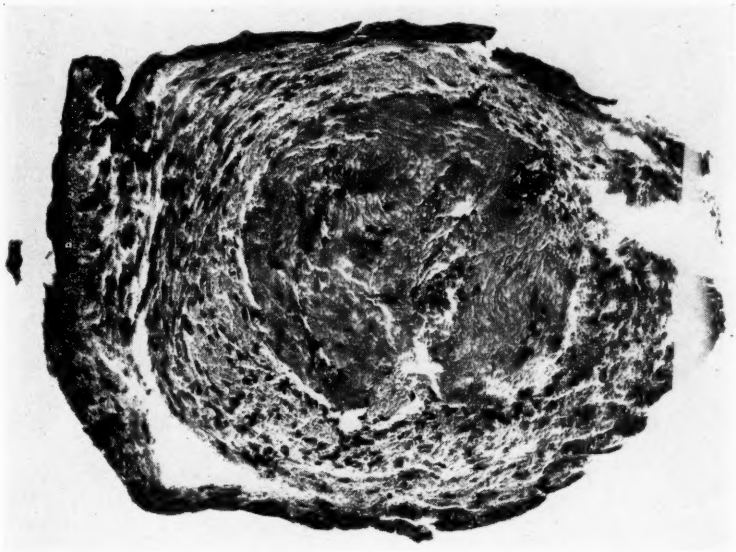

Fig. 2.—Section from a myometrial fragment cultivated in vitro for 30 days. In color the fragment showed a capsule of active red-staining cells from which the proliferating cells migrated enclosing dense blue inactive connective-tissue elements. (Bouin's fixative. Masson trichrome stain. ×50.)

more abundant in myomas. Although these differential staining studies appear to indicate a smooth-muscle origin for the proliferating cells, we have not ruled out the possibility that active connective-tissue cells may change their staining reaction from blue to red and undergo proliferation. In fact, in correlative studies of this type employing embryonic and adult fibroblast cultures, we have found that the periphery of an explant as well as the proliferating cells take the red stain. It is doubtful, therefore, whether further experimentation along these lines would be profitable.

We have recently employed the cover-glass roller-tube method of cultivation in order to facilitate the study of detailed cellular morphology and, also, to permit differential staining of the outgrowing cells. However, the growth observed in these cover-slip cultures does not appear to be as profuse as that seen in cultures grown directly on the glass of test tubes. Perhaps the round surface of the roller tube is more conducive to multiplication because of a more complete washing action by the supernatant nutrient fluid. Nevertheless, this reduced cellular multiplication which occurs in cover-slip cultures is actually

highly desirable in identification studies since it permits the competitive phenomenon of progressive cellular differentiation. Indeed, in order to facilitate more complete differentiation of cell types we have recently initiated the practice of removing chick embryonic extract from the nutrient formulas after sufficient cellular proliferation has occurred.

Fig. 3.

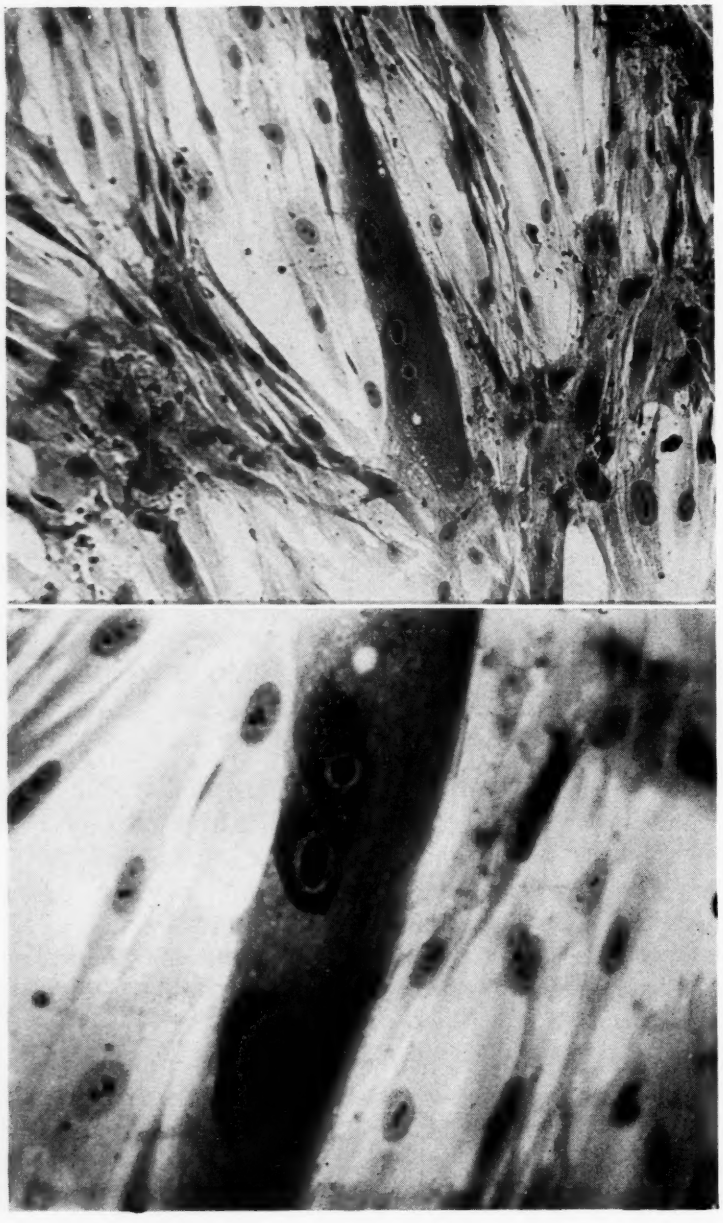

Fig. 4.

Figs. 3 and 4.—Outgrowth from myometrium after 32 days' cultivation demonstrating a large multinucleated and striated cell not of the fibroblast-like type. (Bouin's fixative. Masson trichrome stain. (×75 and ×150.)

In differential-staining studies we have observed that the proliferating cells, regardless of the state of differentiation, always take various shades of red, the so-called muscle stain. As mentioned previously, this result is not particularly significant, since proliferating fibroblast cultures from embryonic and adult tissue also stain red. However, certain cells in these cultures stained a darker red and their cellular morphology was not consistent with that seen in fibroblast-like cell types. As an example, the large dark-staining multi-

Fig. 5.

Fig. 6.

Figs. 5 and 6.—Spindle-shaped cells from the same slide as Figs. 3 and 4, apparently showing longitudinal striations. (×360.)

nucleated cell illustrated in Fig. 3 is definitely not a fibroblast. This cell appears to be undergoing amitotic division and the halo surrounding the chromatin material apparently signifies active protein synthesis. In addition, at higher magnification, this cell reveals longitudinal striations which may or may not be myofibrils (Fig. 4).

Perhaps of more importance are the fibrils seen in the more frequently observed fibroblast-like type of cells (Figs. 5, 6). Although these striations at times run in directions not exactly parallel to the cell and, thus, might be considered to be tonofibrils or fibroglia fibers, we have not, up to the present time, seen such striae in cultures of embryonic and adult fibroblasts fixed and stained by this method. Longitudinal striations are considered to be the most important differentiating morphological feature of embryonic or adult smooth muscle. European workers have noted similar striations in stained cultures of embryonic smooth muscle cultured in vitro and have used the term myofibrils to describe them.

Fig. 7.—Mitochondrial pattern of proliferating cells from myometrium cultured for 22 days in a complete nutrient fluid and then for 10 days in a medium devoid of chick embryonic extract. (Fixed with 10 per cent formalin. Modified Hortega silver carbonate stain. ×360.)

In an attempt to obtain more precise staining of these striations we employed a modified Hortego silver carbonate stain. Apparently the striations were not stained as effectively by this method as by the Masson trichrome technique. However, as shown in Fig. 7, the cytoplasm of the cells was completely filled with filamentous mitochondria of various sizes. In certain cells, the mitochondria extended beyond the ends of the spindle-shaped cells. Although this type of mitochondrial pattern is not specific for muscle cells, fibroblasts usually are characterized by a smaller number of filamentous or granular mitochondria found primarily near the nucleus in stained mounts. Some workers in this field believe that the mitochondria may result from the breaking up of the myofibrils at a certain stage of muscle-cell development. If this

viewpoint is correct then the tandem arrangement of the mitochondria, especially at the edges of the cells as shown in Fig. 7, suggests a muscle-cell origin for these cells.

In studies concerned with experimentally forced differentiation by removal of chick embryonic extract from the nutrient fluid after successful cell proliferation, we consistently found that the cells became extremely narrow and elongated. A comparison of Fig. 3 with Fig. 8 will illustrate this morphological alteration in cell structure. In additon, cellular multiplication virtually stopped a few days after chick embryonic extract was removed. No apparent increase in the number of cells showing longitudinal striations was observable in these cultures. Nevertheless, the altered morphology of these cells toward elongated narrow types and the complete absence of collagen fibers in such cultures are observations which are highly suggestive of a muscle-cell type.

Fig. 8.—Elongated nature of the proliferative outgrowth from myometrium cultivated for 22 days in a complete nutrient fluid and then for 10 days in a medium devoid of chick embryonic extract. (Bouin's fixative. Masson trichrome stain. ×75.)

At the present time we are unable to draw definite conclusions regarding the positive identity of the proliferating cell types seen in our myometrial and myoma tissues grown in vitro. However, we believe that sufficient progress in the identity study has been made to justify presentation of this report with the hope that it may stimulate others not only in the identification of smooth-muscle cells from fibroblasts, but also in employing this and other methods of search for the factors responsible for the growth of uterine fibroids (myomas) in vivo.

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THE TREND IN CESAREAN SECTION IN RECENT YEARS*

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Dieckmann [1] (Chicago Lying-in Hospital), in 1950, stated: "Cesarean section performed by a properly trained obstetrician is now a recognized procedure for the management of many obstetric and fetal complications formerly treated by vaginal delivery because the maternal mortality, attributable to the operation itself, is only 0.1 per cent or less. The fetal mortality, ascribable to the operation, is less than 1.0 per cent." The cesarean section incidence at the Chicago Lying-in Hospital from 1942 to 1949 was 5.0 per cent. For the year 1948 the clinic rate was 4.5 per cent and the private rate 7.0 per cent.

D'Esopo[2] (Sloane Hospital), in 1948, stated: "The matter of the cesarean section rate will be of considerable interest in the next five or ten years, for there appears now to be a definite tendency to broaden the indications. The greater safety of the operation makes this obvious." He stated that a certain number of easier midforceps will always be done but predicted that the difficult, traumatic midforceps operations would be relegated to category of the obsolete procedures along with craniotomy, high forceps, version, bags, and bougies. Finally, D'Esopo suggested as a working formula for an obstetric service that deals with an abnormal group a cesarean section rate between 5 and 6 per cent with a maternal mortality of 0.1 per cent and a preventable term fetal loss of 1 per cent. Furthermore, to avoid unwarrantedly high cesarean section rates, he believes that the traumatic deliveries and preventable fetal deaths can each be reduced to a figure under 1 per cent with a section rate of near 6 per cent.

Douglas[3] reported a cesarean section incidence of 4.2 per cent at the New York Hospital for 1951. However, he did not state whether this included private cases.

A number of our teaching institutions in the area of the South Atlantic Association, with large Negro ward services, have very low cesarean rates. On the other hand, it is my impression that many obstetricians in private practice, in this area, have a rather liberal cesarean rate. Therefore, this study of cesarean section at Charlotte Memorial Hospital, where approximately 75 per cent of the patients are private, was undertaken in order to evaluate results.

The Cesarean Section Rate

Charlotte Memorial Hospital began operation in late 1940. The cesarean section rate is higher in this institution than in the other two hospitals located in Charlotte, which is quite understandable because of the availability of a resi-

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dent staff and a good anesthetic staff. Practically all of the private cases are handled by specialists, except for an occasional delivery by the general practitioner. From 1940 to Nov. 1, 1952, 10,093 patients (five months and over) were delivered, with a cesarean section rate of 4.5 per cent. The rate on the ward service was 1.8 per cent and on the private service 5.3 per cent. The rate has been increasing and in 1952 the ward rate was 3.4 per cent and the private rate was 6.4 per cent, the combined rate being 5.6 per cent. The ward service includes all the Florence Crittenton Home cases (almost one-half of the ward service), and this has undoubtedly influenced the low ward rate. Then, too, the staff service seldom sees the long-standing sterility cases, elderly primiparas, bad obstetrical history cases—the so-called "high priority babies" seen frequently in private practice. It must be admitted, however, that there is a reluctance on the part of the attending staff to section a ward patient as readily as a private patient. This situation is improving, as the figures show.

Maternal Mortality

There were two maternal deaths, thus giving a cesarean section mortality rate of 0.44 per cent, uncorrected. (This study does not include one postmortem cesarean section.)

The first fatality which occurred in 1941 was that of a staff patient, aged 14 years, a primipara, who was delivered of a 7 pound, 8 ounce baby after 47 hours of labor (40 hours with ruptured membranes) by a low flap operation, under cyclopropane anesthesia, for cephalopelvic disproportion. The patient developed pneumonia 48 hours after delivery and was transferred to the medical service. The pneumonia was thought to be due to Friedländer's bacillus. The patient died on the thirty-fourth postpartum day. The autopsy report was as follows: "Diffuse, chronic, interstitial pneumonia of both lungs with bronchiectatic abscesses." This case would now very likely have responded to antibiotic therapy.

The second death which occurred in 1948 was that of a private patient, aged 35, para i, gravida v, with a repeat section. The original section was done eight years previously for placenta previa and was followed by a stormy convalescence. There was a history of chronic gastrointestinal disease, and on one occasion ulcerative colitis was found. The obstetrician was worried about the scar and a repeat section was done at eight and one-half months with a suspected dead baby of several days, cause of death not known. A low flap operation was performed under single injection spinal anesthesia, reinforced with Pentothal, with delivery of a 3 pound, 10 ounce macerated stillborn infant. The patient developed diarrhea on the third postpartum day, which was apparently much more serious than was first thought and which persisted until death on the sixth day. The autopsy revealed an ulcerative colitis. The pathologist reported: "It cannot definitely be stated whether the ulcerative colitis was present prior to the operation. The cause of death is not quite clear inasmuch as ulcerative colitis per se, unless part of generalized septicemia, as a rule does not cause death within a few days. Whether the operation or pregnancy should be considered an additional factor is uncertain." I might add that there was no evidence of septicemia or peritonitis. The record seems to indicate that intensive treatment with the proper fluids and electrolytes was instituted too late. However, cesarean section with a known dead baby, even if for repeat section, may be inviting trouble and probably should rarely be done except in cases of severe bleeding which cannot be controlled otherwise.

A number of clinics, including the Chicago Lying-in Hospital,[1] New York Hospital,[3] and Sloane Hospital,[2] have reported over 1,000 consecutive cesarean sections without a maternal death attributable to the operation. Dieckmann[1]

states: "Obviously death from infection, the principal cause of mortality following cesarean section up to 1940, must now be considered the result of error in judgment or faulty operating room technique." Certainly the safety of cesarean section has been well established.

Types of Operation

There were 228 low flap sections, 225 classical, and 5 extraperitoneal. Adhesions were present following the classical operation almost twice as often as after the low flap, and morbidity was about evenly divided between the two types. However, of the past 5,000 (approximate) deliveries, only 11 per cent of the primary sections for disproportion were classical in contrast to 67 per cent classical in the preceding 5,000 (approximate) deliveries. This trend is as it should be. Some of us practically never do the classical operation. Likewise the extraperitoneal operation is seldom, if ever, indicated in our experience.

Morbidity

The uncorrected morbidity rate was 15 per cent, based on a temperature of 100.4° F. or more for any two days after the first postpartum day. (If only the first postpartum day is excluded, the morbidity rate is 29 per cent.) It was 40 per cent for the extraperitoneal cesareans, 16 per cent for the low flap, and 13 per cent for the classicals, as one would expect. The very frequent use of antibiotic and chemotherapeutic drugs, improved supportive therapy, maintenance of fluid and electrolyte balance, transfusions, improved operative techniques and anesthesia, early ambulation, etc., have helped greatly in preventing morbidity and mortality.

Indication for Cesarean Section

Table I shows the indications for section. Of the 458 sections, 215 (47 per cent) were done for disproportion. There was no fetal mortality in the group of primary sections for disproportion. In the 83 repeat sections done for disproportion originally, there was a corrected fetal loss of one baby, resulting from a repeat section done too early with loss of the premature baby. Furthermore, there was no fetal mortaliy, after correction, in the prolonged labor-uterine dysfunction group (23 cases). Thus, the results indicate that cesarean section was done before fetal damage occurred and this is as it should be!

Landesman,[4] of the New York Hospital, has pointed out that the fetal risk associated with initial section for dystocia is extremely low, whereas repeat sections entail further risk such as miscalculation of the expected date of confinement with resulting prematurity, occasional rupture of a uterus early in the third trimester, and general anesthesia coupled with unknown prematurity.

In the 59 remaining repeat sections done for conditions other than disproportion, there was one fetal death (corrected) which was in connection with a "hysterotomy" for toxemia of pregnancy at five and one-half months.

The repeat sections slightly exceeded the number of primary sections done for disproportion. It is obvious that our staff feels that, as a rule, "once a

cesarean always a cesarean." Actually only 11 patients were allowed vaginal delivery following section, 5 of which were personal cases. Thirty-eight and seven-tenths per cent of the women who have had previous sections at the New York Lying-in Hospital[3] and 35.8 per cent at the Margaret Hague Maternity Hospital[5] are delivered vaginally. This would suggest that we should allow more of our patients to deliver vaginally.

TABLE I. INDICATIONS FOR CESAREAN SECTION

INDICATIONS		NUMBER	PER CENT
Previous section (including 83 for disproportion)		142	31
Cephalopelvic disproportion	104	132	29
Breech disproportion	28		
Toxemia		44	10
Placenta previa		38	8.0
Premature separation		26	6.0
Prolonged labor Inertia (uterine dysfunction) Cervical dystocia		23	5.0
Vaginal plastic		9	2.0
Fetal distress		7	1.5
Diabetes		7	1.5
Elderly primipara		4	0.9
Cardiac Disease		3	0.7
Others		23	5.0
Total		458	

Cosgrove[5] states: "The incidence of catastrophic rupture of the uterus is low . . . recent experience does not indicate that rupture of the scar of a previous incision in the uterus is always as catastrophic as earlier experience would indicate . . . particularly if the rupture is through a low segment incision." This agrees with our limited experience. We have had four cases, all with incomplete ruptures, and all babies surviving. Three of these patients had previous classical sections and the ruptures were discovered at the time of elective repeat section. The fourth, a grand multipara, had a low flap section previously and had incomplete rupture following labor of one hour. Cosgrove[5] has stated that there is no method of accurate prediction of impending rupture of the uterus.

It is of interest that 7 cases of uterine constriction ring were found at section.

Primary Cesarean Section for Cephalopelvic Disproportion.—

Table II shows that the incidence of primary section for cephalopelvic disproportion is increasing due to two reasons, namely, election of cesarean section rather than difficult traumatic midforceps delivery, and more frequent use of cesarean section for breech presentation rather than risking fetal trauma from vaginal delivery.

It has been only a few years ago that obstetricians took great pride in doing well a hard midforceps delivery. On occasions one had to be quite skilled in the art of forceps delivery since there was not much choice, regardless of the trauma, both maternal and fetal. Today in our hospital most of these patients are being delivered by section. In general, we are replacing the difficult, traumatic midforceps operation with cesarean section. (We are still doing midforceps but mostly low midforceps.) D'Esopo has shown that by increasing the cesarean section rate at Sloane Hospital to 6 per cent, the difficult midforceps operation has been practically eliminated with a corresponding decrease in preventable term fetal deaths to 1 per cent. Comparable figures are not yet available from Charlotte Memorial Hospital, but the trend (see Table IX) is the same since we have had almost a 50 per cent reduction in fetal mortality in the past five years. In 1951 and 1952 the preventable term fetal deaths, as well as the number of traumatic vaginal deliveries, were both below 1 per cent.

TABLE II. PRIMARY CESAREAN SECTION FOR CEPHALOPELVIC DISPROPORTION (132 CASES)

	1940-1947 (4,845 DELIVERIES)	1948-1952 (5,247 DELIVERIES)
Total number	58 (including 4 breech)	74 (including 24 breech)
Fetal mortality	0	0
Trial or test of labor	22 (38%)	36 (49%)
Under 6 hours	6 cases	8 cases
6-12 hours	7 cases	8 cases
12-24 hours	7 cases	10 cases
Over 24 hours	2 cases	10 cases
No labor	36 (62%) including 2 breech	38 (51%) including 16 breech
X-ray	22 (38%)	54 (73%)
Classical section	39 (67%)	8 (11%)
Low flap	18 (31%)	64 (86%)
Extraperitoneal	1	2
Morbidity, uncorrected	13	8

A trial or test of labor has been used in recent years in approximately one-half of the cases. The group sectioned electively without any labor included 16 patients with breech presentations. A trial labor has been used by our staff more or less in the way described by D'Esopo,[2] namely, more for the purpose of ascertaining the efficiency of uterine contractions over a period of from 8 to 12 hours following the onset of regular contractions rather than to determine the adequacy of the pelvis by a full test of labor. A full test of labor was given in a number of cases, and this is being done more frequently at present. However, review of the records shows that frequently the decision is made to section after trial labors of six to eight hours when the cervix is not dilated over 1 to 2 cm. It is my opinion that this type of "trial labor" is of little value. It determines neither the efficiency of uterine contractions nor the adequacy of the pelvis. Such a patient might as well be sectioned electively. The only advantage I can think of is that it makes the low flap operative technique somewhat easier. It was also observed that large babies were found not infrequently

in cases of trial labor ending in section, which was suggestive that in these cases uterine inertia (dysfunction) was probably the chief factor rather than disproportion. However, both factors were undoubtedly responsible in some cases.

Pelvic x-ray studies have been used considerably more often (73 per cent) in the past five years. However, this should be 100 per cent. Every woman having a primary section for disproportion deserves a careful x-ray study! X-ray prognosis is far more accurate than clinical estimation alone. If one has to make the decision between accepting clinical findings or x-ray findings in suspected or actual cephalopelvic disproportion, one will make fewer mistakes by accepting the x-ray findings, provided the obstetrician understands the x-ray technique employed and properly interprets the films for himself. This represents my own experience of 12 years, using the Caldwell-Moloy technique without a precision stereoscope. I have found x-ray studies to be sufficiently accurate, and of absolute necessity in reaching a decision as to the proper method of handling the case of disproportion.

Moloy[6] in his recent excellent monograph states: "If the clinical course of labor is used to determine disproportion, without x-rays, there will be some patients unfortunate enough to develop extremely powerful labor in the presence of great disproportion, and the child may be born by a 'spontaneous' delivery with serious injury." Moloy[6] stresses the fact that a considerable degree of disproportion may be overcome by permitting prolonged labor. He states: "In fact, many clinics in this country and in Europe employ this method of treatment and report a low incidence for cesarean section. Only patients who present evidence of severe pelvic contraction by pelvic examination are treated by cesarean section. In a sense, x-ray studies are superfluous in the management of labor by this policy. . . . It is not unusual to observe proven instances of high degrees of disproportion in which a normal delivery has resulted from an efficient labor and marked molding. Torpin in his recent textbook illustrates case studies to prove this point. . . . However, there is reason to doubt the advisability of allowing delivery from below under these circumstances, for fetal death from laceration of the tentorium has followed *spontaneous* delivery. . . . We know that babies may survive intracranial damage as shown by bloody spinal taps and other clinical manisfestations. In addition, our knowledge is incomplete regarding the follow-up mental status of a child subjected to the degree of molding required to permit delivery with such high degrees of cephalopelvic disproportion. The mother's soft parts sustain injury and it is suspected that cystocele and rectocele and prolapse of the uterus are more commonly encountered in patients who have been delivered under these conditions."

Kaltreider[7] has even proposed that there should be a trial of labor and/or trial forceps delivery in all pelves with vertex presentations without previous cesarean section. At least this approach clearly indicates how safe cesarean section is considered to be at present! However, I must completely disagree with his proposal. At the Fifth American Congress on Obstetrics and Gynecology, in 1952, Moloy, in his discussion of Kaltreider's paper,[7a] said: "Obviously the best interest of the patient is not served if the decision to perform

cesarean section is delayed until full dilatation or after a trial at forceps—a heroic procedure mentioned to be condemned except in unusual circumstances and never as a planned method of diagnosis."

I will agree, in general, to the following of Kaltreider's proposals: (1) Clinical pelvimetry is definitely inadequate. Roentgen pelvimetry adds appreciably to our knowledge, but is unable to give a completely accurate prognosis. The obstetrician should learn to interpret films himself and not to rely on the roentgenologist. (2) Greater use should be made of trial labor in both inlet and midplane contractions. (3) In breech presentations the decision for vaginal or abdominal delivery should probably be made before the onset of labor, with the right to interfere abdominally when uterine inertia or lack of progress is apparent.

Undoubtedly more patients in our series should have had adequate trials of labor. On the other hand, errors in judgment were made in some patients who did have an adequate trial of labor in that forceps delivery, which turned out to be difficult and traumatizing, was selected rather than cesarean section. After such a delivery the obstetrician might wish that he had performed cesarean section, and, in retrospect, he might decide that the clinical and x-ray findings were sufficiently accurate to have indicated section in the first place.

Incidentally, 7 patients in our series, who had unsuccessful attempts at vaginal delivery by forceps, were sectioned. The babies were undamaged. However, these cases were "unusual circumstances," as described by Moloy.

Primary Cesarean Section for Breech Presentation (Disproportion and/or Inertia).—

Table III shows that the incidence of primary cesarean section for disproportion and/or inertia in breech presentation has doubled in the past five years. However, during the same period there have been only 3 term fetal deaths (out of 216 total breech deliveries), in contrast to 10 term fetal deaths (out of 132 total breech deliveries) in the preceding period. Therefore, we feel that the increased section incidence is entirely justified. We believe that the increased section incidence was largely responsible for this reduction in fetal mortality. It is, of course, well known that x-ray estimation of the size of the head in breech presentation is not accurate enough to be of practical value. In the past five years, in 16 out of 24 cases of section in breech presentations there had been no trial of labor. Delay in the descent of the breech during labor may indicate disproportion and be an indication for section.

TABLE III. PRIMARY CESAREAN SECTION FOR BREECH PRESENTATION (DISPROPORTION AND/OR INERTIA)

	1940-1947 (4,845 DELIVERIES)	1948-1952 (5,247 DELIVERIES)
Cesarean Section Rate	6.0%	12.0%
Total number term (2,500 gram and over) fetal deaths, *all deliveries,* uncorrected	10	3

Toxemia of Pregnancy.—

Toxemia of pregnancy was responsible for 12 fetal deaths and was a factor in 2 others. Only one baby out of the 14 weighed 2,500 grams or over. Thus, in respect to prematurity, the toxemia fetal mortality is similar to the great number of placenta previa deaths. Our staff has great respect for toxemia, having learned through bitter experience. While the fetal mortality is high we feel that early interruption of pregnancy is indicated for the mother's safety and future well-being. Recent experience would, however, indicate that the cesarean incidence may be lowered by use of the repeated intravenous Pitocin drip method of medical induction in selected cases.

Placenta Previa and Accidental Hemorrhage.—

There has not been a maternal death due to placenta previa or accidental hemorrhage, either by vaginal delivery or by cesarean section, in this series of 10,093 deliveries. However, the fetal mortality for the placenta previa group is entirely too high. D'Esopo,[2] in his Sloane study (1942-1947), reported a 13 per cent cesarean fetal mortality. Williamson, Greeley, and Schleicher[4] reported a cesarean fetal mortality rate of 12 per cent from the New York Hospital from 1932-1948. On the other hand, Bysshe,[8] in his Sloane study of accidental hemorrhage (1933-1949), showed a 45.4 per cent cesarean fetal mortality, whereas our mortality was 35 per cent. Likewise O'Regan and Landesman[4] reported a cesarean fetal mortality rate at New York Hospital from 1932 to 1942 of 53 per cent and from 1942 to 1948 of 40 per cent.

TABLE IV. PLACENTA PREVIA AND ACCIDENTAL HEMORRHAGE

Cesarean section for placenta previa	38 (61% of all placenta previa cases)
Cesarean section fetal mortality	14 (37%)
Cesarean section for accidental hemorrhage	26 (20% of all accidental hemorrhage cases)
Cesarean section fetal mortality	9 (35%)

Six (67 per cent) of the 9 deaths in connection with accidental hemorrhage were stillbirths (5 were known fatalities before section), whereas only 2 (14 per cent) of the 12 placenta previa fatalities were stillbirths. There was only one term (by date) death in either group. Thus the problem resolves itself largely into that of prematurity. For example, 10 of the 14 placenta previa deaths were in babies weighing 4 pounds, 6 ounces and less (7 of these weighed 3 pounds, 5 ounces and less). Likewise, Acken,[9] in his study at the Methodist Episcopal Hospital, Brooklyn, N. Y., found that prematurity associated with placenta previa was the most common cause of fetal death. Review of the records indicates that, in many of these cases, pregnancy could have been prolonged with the patient under careful observation and perhaps without undue risk. With the ready availability of blood today, obstetricians should carry these cases nearer term and thus prevent the toll exacted by prematurity itself. Another aspect of prematurity is that of better nursery care. It has been demonstrated repeatedly that the premature survival rate rises with the adequacy of premature nursery setup and the quality of nursing personnel. By stressing this, we have had a higher fetal survival rate among prematures in recent years.

Our staff feels that the treatment for placenta previa is largely cesarean section. In the past seven years section has been used in 69 per cent of all cases of placenta previa. On the other hand, it was used in only 18 per cent of all accidental hemorrhage cases during this same period. However, contrary to the recent trend in many hospitals, in 1952 we used cesarean section in 30 per cent of our cases of accidental hemorrhage. Our staff feels that section is indicated in the interest of the mother in severe abruptio, whereas some of the staff feel that it is also indicated in the interest of the baby in some of the less severe cases, i.e., those in which bleeding *continues* but is usually not enough to cause signs of shock in the mother (or if present, mild), and usually without signs of fetal distress. In these cases labor is mild or absent and the cervix is closed or dilated very little. There is great concern for these babies. The mother is given oxygen continuously throughout the period of observation and during operation until the baby is delivered. It is usually too late to wait until definite, certainly severe, fetal distress is present before electing section. Occasionally, however, one has to take this chance and section anyway in the presence of early fetal distress in the effort to obtain a live baby.

Admittedly, there is no way clinically to be sure how much separation has taken or will take place. Each case has to be individualized. Many can be successfully handled by simple rupture of the membranes. However, the important thing, as pointed out by Bysshe,[8] in an exhaustive review of accidental hemorrhage at Sloane Hospital, is that even the cases of mild or moderate placental separation carry a high fetal mortality. He estimated that 20 per cent of their intrapartum fetal deaths might have been prevented by more radical treatment, either through less delay in vaginal delivery or by earlier election of cesarean.

Hellman[10] in a discussion of Bysshe's paper stressed the fact that the mild cases have an extremely high fetal mortality rate, and that it is in this group that marginal separation with rupture of the marginal sinus occurs. He felt that the day would come when more sections would be done for antepartum hemorrhage than are now considered justifiable.

Infant Mortality in Cesarean Section

In a review of the literature, there is a surprising discrepancy in the standards used by various authors in infant mortality studies. Some use only term babies (2,500 grams and over), some use 1,500 grams, some use 1,000 grams and even lower. Adair[11] has suggested 750 grams as the weight limit between previability and viability. Others use the estimated date of seven months and over. Perhaps it would be more nearly correct to exclude all cesareans under seven months (i.e., hysterotomies); however, an occasional baby delivered before this estimated date does survive. Therefore, I have shown the mortality for various groups even including the group five months and over, since the latter corresponds to the age of reportable births in North Carolina. Furthermore, any baby who did not survive 30 days was considered a mortality. D'Esopo,[19] in a personal communication, has recently suggested that all operations in which the fetus weighs 500 grams or more be called cesarean sections and that all those in which the fetus weighs less than 500 grams be called hysterotomies.

Admittedly, the gross fetal mortality rate of 10 per cent is high, particularly when compared with the 3.9 per cent gross vaginal delivery mortality rate. However, the corrected figures give the true picture. As pointed out by D'Esopo,[2] the uncorrected fetal mortality is sometimes erroneously used as evidence that the risk to the baby in cesarean section is great and that cesarean actually offers a false sense of security for fetal survival. D'Esopo's[2] study of the fetal deaths revealed that in most of the cases the cause of death was inherent in the maternal complication for which the operation was performed. The same is true in this study. For example, of the 46 fetal deaths, in only 2 can the operation itself be blamed. In one a repeat section for disproportion was done too early because of uncertainty about the expected date of confinement. In the other a case of toxemia was interrupted three weeks from term but a 6 pound, 2 ounce baby survived only 34 hours with atelectasis, with autopsy revealing "hyaline-like membrane." Incidentally, this case was the only one of the entire series diagnosed as "hyaline-like membrane," but it is possible that a few of the early cases could have been so diagnosed in the light of our present knowledge.

TABLE V.* GROSS INFANT MORTALITY, 46 CASES
(INCLUDES ALL DEATHS FIVE MONTHS AND OVER)

MATERNAL CAUSES	FETAL CAUSES		TERM	PREMATURE	STILLBIRTH	NEONATAL DEATH	TOTAL NUMBER
Toxemia	Prematurity	12	1	13	0	14	14
	Hyaline membrane	1					
	Virus diarrhea	1					
Placenta previa	Anoxia	3	1	13	2	12	14
	Prematurity	11					
Accidental hemorrhage	Anoxia	6	1	8	6	3	9
	Prematurity	3					
1 Extraperitoneal section (prolonged labor) 1 Repeat section	Congenital defect		2		1	1	2
2 Repeat sections	Virus diarrhea	2	2			2	2
Genitourinary tract disease	Prematurity	2		2		2	2
Repeat section too early	Prematurity	1		1		1	1†
Breech with fetal distress	Anoxia	1	1			1	1
Repeat section	Macerated fetus, antepartum death, cause unknown			1	1		1

*From original table outlined by D'Esopo.[2]
†Error in date, repeat section.

In the remaining 44 cases, cesarean section was not the cause of death in so far as could be determined. However, 28 infants were premature and it is only fair to state that the choice of anesthesia was not always good in these

cases, and the use of sedation and preoperative medication was open to criticism in some cases. These factors must have played a considerable part in fetal mortality. It should be remembered, however, that the same factors

TABLE VI. GROSS INFANT MORTALITY BY WEIGHT, 46 CASES

NUMBER OF CASES				
UNDER 1,000 GRAMS (2 POUNDS 3 OUNCES TO 3 POUNDS 5 OUNCES)	1,000-1,500 GRAMS (2 POUNDS 3 OUNCES TO 3 POUNDS 5 OUNCES)	1,500-2,000 GRAMS (3 POUNDS 5 OUNCES TO 4 POUNDS 6 OUNCES)	2,000-2,500 GRAMS (4 POUNDS 6 OUNCES TO 5 POUNDS 8 OUNCES)	2,500 GRAMS AND OVER (5 POUNDS 8 OUNCES)
6	12	10	8	10

could have played a similar role had vaginal delivery been selected, plus the greater maternal risk. The fetus was dead before section in 7 cases, 2 died of congenital anomalies, and 3 died of virus (epidemic) diarrhea. Four cases of anoxia resulted from maternal complications for which section was done.

Ten (22 per cent) of the 46 deaths were in the 2,500 gram and over group, yet 2 were known fetal deaths in severe accidental hemorrhage, two were in infants with congenital anomalies incompatible with life, and two were neonatal virus (epidemic) diarrhea deaths, thus leaving 4 cases, or a corrected mortality rate of 1.0 per cent for this weight group. However, of the 4 cases, one, a breech, had marked fetal distress before section. A second, a case of placenta previa, in which induction of labor, including rupture of the membranes, was unsuccessful, finally terminated in section as a "last resort." Now technically both these cases have to be included in cesarean fetal mortality, but it should be understood that cases of this sort serve to make the cesarean fetal mortality appear too high.

TABLE VII. GROSS INFANT MORTALITY BY WEIGHT AND/OR DATE

FIVE MONTHS AND OVER	SEVEN MONTHS AND OVER	1,000 GRAMS AND OVER	1,500 GRAMS AND OVER	2,000 GRAMS AND OVER	2,500 GRAMS AND OVER	2,500 GRAMS AND OVER CORRECTED
10%	6.6%	8.8%	6.4%	4.3%	*2.6%*	*1.0%*

TABLE VIII. COMPARISON OF CESAREAN SECTION GROSS INFANT MORTALITY

HOSPITAL	YEARS	SECTION RATE (%)	1,000 GRAMS AND OVER (%)	1,500 GRAMS AND OVER (%)	1,500-2,500 GRAMS (%)	2,500 GRAMS AND OVER (%)
Charlotte Memorial	1940-1952	4.5	8.8	6.4	32	2.6
Duke University (Creadick)	1939-1948	1.8 (term only)				9.2
New York Hospital (Landesman)	1939-1943	3.3 (1941-1945)		8.3	40	5.5
	1944-1949	4.0 (1944-1948) 4.4 (1948) 3.8 (1949)		6.3	22	4.4
Chicago Lying-in (Dieckmann and Seski)	1942-1949	5.0	5.9			

Seventy-eight per cent of the total deaths were in the group of infants weighing less than 2,500 gram (39 per cent less than 1,500 grams, 13 per cent less than 1,000 grams). Thus it is obvious that to reduce fetal mortality, we have to *concentrate* on the premature group.

On a comparative basis, Creadick[12] in 1949 reported a gross section fetal loss of 9.2 per cent in babies of 2,500 grams and over, at Duke from 1939 to 1948; whereas, our gross section fetal loss was 2.6 per cent in babies of 2,500 grams and over. However, our total incidence of cesarean section is 4.5 per cent against a rate of 1.8 per cent (in deliveries of infants that weigh 2,500 grams and over) at Duke. Naturally this would make a difference in the fetal mortality rate since their group must of necessity be the group with only the most severe pathology.

Landesman[4] in 1951 reported a section fetal mortality rate from New York Hospital in babies weighing 1,500 grams and over, of 8.3 per cent from 1939 to 1943 and 6.3 per cent from 1944 to 1949. Our mortality for this group was 6.4 per cent. New York Hospital's mortality rate for full-term (2,500 grams and over) infants from 1939 to 1943 was 5.5 per cent and from 1944 to 1949 was 4.4 per cent. Our mortality rate for this group was 2.6 per cent. New York Hospital's mortality rate for the premature group (1,500 to 2,500 grams) from 1939 to 1943 was 40 per cent and from 1944 to 1949 was 22 per cent, whereas our rate for this group was 32 per cent.

Dieckmann and Seski[1] in 1950 reported a cesarean fetal mortality rate from Chicago Lying-in Hospital in babies that weighed 1,000 grams and over of 5.9 per cent from 1942 to 1949. Our mortality rate for this group was 8.8 per cent.

TABLE IX. COMPARISON OF THREE PREVIOUSLY REPORTED SERIES WITH PRESENT GROUP

PLACE		CESAREAN SECTION INCIDENCE (PER CENT)	TOTAL DELIVERIES, SEVEN MONTHS AND OVER	GROSS FETAL LOSS, ALL DELIVERIES (PER CENT)
Emory University (ward)		0.5	17,421	3.0
Army Hospital (Ft. Bragg)		0.4	1,699	2.0
Private practice		1.3	2,015	1.9
Charlotte Memorial Hospital (ward and private)	1940-1947	3.9	4,775	3.0
	1948-1952	4.9	5,173	1.6

Colvin[13] at this meeting in 1951 reported a gross fetal loss in 21,135 total deliveries for three separate services conducted by conservative obstetric practice (cesarean rate of 0.5 to 1.3 per cent) counting all infants of seven months and over, of 1.9 per cent to 3 per cent (Table IX). Comparable figures from Charlotte Memorial Hospital from 1940 to 1947 with 4,775 deliveries and a cesarean rate of 3.9 per cent showed a fetal mortality rate of 3.0 per cent. However, from 1948 to 1952, with 5,173 deliveries and a cesarean rate up to 4.9 per cent, there was a drop in fetal mortality to 1.6 per cent. Thus in our experience a more liberal use of cesarean section has been accompanied by a decrease in fetal mortality of almost 50 per cent.

Anesthesia

All anesthesia has been given by registered nurse anesthetists, who are supervised by a certified physician anesthetist. He personally gave all of the spinal anesthesias.

From 1940 to 1945 general anesthesia, mostly cyclopropane, was used. Since 1946 spinal has been used considerably, and in recent years Pentothal Sodium also has been used frequently. Local Novocain, usually in combination with Pentothal, after delivery of the baby, is being used rather frequently at present. More fetal deaths have occurred with general anesthesia than any other type. However, it is difficult, if not impossible, to say how much part the anesthesia played. In several cases, the anesthesia plus heavy preoperative sedation in a premature may have been decisive. Necessity for, and difficulty in, resuscitation occurred not infrequently when a general anesthesia was used. However, it is alarming that 34 per cent of the infants born with Pentothal anesthesia or Pentothal combinations required some degree of resuscitation. In some cases the respiratory depression was mild but in 50 per cent of the cases prolonged resuscitation was necessary. A number of these (Pentothal) babies were delivered in 5 or 6 minutes, most within 8 minutes, and all within 12 minutes. It is interesting that 1 out of 3 term babies delivered under Pentothal alone required resuscitation, and 2 out of 2 prematures; 9 out of 17 term babies delivered under Pentothal-cyclopropane required resuscitation, and also 1 premature, while only 2 out of 21 Pentothal-nitrous oxide or ether required resuscitation, and 2 out of 5 prematures; and none out of 6 Pentothal-nitrous and cyclopropane required resuscitation, but all 3 prematures did. This would suggest that perhaps Pentothal, nitrous oxide, and ether is the safest of the Pentothal combinations for cesarean section.

TABLE X. TYPE OF ANESTHESIA

ANESTHESIA	NUMBER	BABIES NEEDING RESUSCITATION
Cyclopropane	125	13 (10%)
Nitrous oxide, ether, cyclopropane combinations	66	9 (14%)
Pentothal Sodium and Pentothal combinations	58	20 (34%)
Local Novocain, and Novocain combinations	47	5 (11%) (no cases from local Novocain alone)
Spinal		
Single injection (50-75 mg.)	78	6 (5%)
Continuous	84	4 (5%)
Total	458	

Hershenson[14] says Pentothal can produce "obstetric anesthesia when a state of acute barbiturate toxicity is induced. . . . The maternal and fetal blood barbiturate concentrations are equal within approximately ten minutes of maternal intravenous administration." Hershenson further states that the incidence of neonatal asphyxia has been increased in their experience at the Boston Lying-in Hospital using the nonvolatile (i.e., Pentothal) drugs.

This study points out that Pentothal, either alone or in combination, may produce a dangerous degree of asphyxia in the baby, even when delivery takes place within 5 or 6 minutes. This is particularly true when the cesarean is done for bleeding, or for fetal distress, or when the baby is premature. Certainly it is inviting respiratory depression and severe asphyxia to give the patient who has had considerable sedation either Pentothal or general anesthesia. The same warning holds for patients who are bleeding, in or approaching shock, having fetal distress, or whose babies are premature, etc.

One patient had a respiratory failure shortly after Pentothal was started just before uterine incision. She responded to artificial respiration and the baby was all right. Had the Pentothal been administered at the beginning of the operation, the outcome would probably have been a fetal death.

Montgomery[15] stated that, due to the possible complications, he did not feel that Pentothal was very reliable or a very safe anesthesia for cesarean section. He stated: "I prefer to limit the use of Pentothal to supplementing other forms of anesthesia, and I am not completely happy about even that."

Continuous spinal anesthesia produced a drop in blood pressure in 14 per cent of the cases and single injection spinal in 4 per cent. Although the acute hypotension was marked in some cases, it was quickly corrected and no apparent harm resulted to either baby or mother. Patients who have had long, exhausting labors are more likely to experience a drop in pressure. Very occasionally an immediate blood pressure elevation is experienced, along with severe headache as soon as the needle is introduced. Occasionally continuous spinal anesthesia fails to work in certain cases. Postspinal headache was recorded as present in at least 10 per cent of the continuous spinal cases. The incidence seems much higher and furthermore it seems to be increasing. This is a most annoying complication, and at times gets to be quite severe. We have found no effective practical remedy thus far. New smaller gauge needles, 24 or 26, may be of value.

Single injection spinal, frowned upon in many quarters, has worked well. The average dosage is 50 to 60 mg. (Novocain) and the maximum 75 mg. Anesthesia is produced for an average time of one hour.

The powerful sustained uterine contractions that may develop under spinal anesthesia, as described by Malpas, Ward, Anz, and McCarthy,[18] although not experienced in our series, should be kept in mind.

Finally, local anesthesia, although exacting, requiring patience and gentleness on the part of the operator, and not liked too well by most patients, is the safest of all anesthetic agents for cesarean section. In the words of Douglas and Landesman[16]: "No other anesthesia is as safe or has as few complications."

Summary and Conclusions

A study of cesarean section at Charlotte Memorial Hospital shows that the incidence has increased and suggests that a rate of near 6 per cent in this institution is adequate. There has been a corresponding reduction in both the traumatic vaginal deliveries and the preventable term fetal deaths to a figure under 1 per cent (as originally shown by D'Esopo). The ward cesarean sec-

tion rate which has been disproportionately low, due in part to Crittenton Home cases, is increasing. The problems of the private patient are frequently different from those of the ward patient and should be so recognized. However, where the obstetrical indication is the same, cesarean section should be done as readily in the ward patient as in the private patient.

The safety of cesarean section for the mother has been established. It is based on increased obstetrical knowledge resulting in better selection of cases, improvement in operative and anesthetic techniques, proper use of blood, fluids, and electrolytes, supportive therapy, antibiotic and chemotherapeutic drugs, and early ambulation. In this series, in all probability, neither of the two maternal deaths (0.44 per cent) would have occurred today.

The low flap operation is replacing the classical section. The morbidity rate is low. There were 4 incomplete ruptures of the uterus.

The chief indications were repeat sections, cephalopelvic disproportion, toxemia of pregnancy, hemorrhage, and prolonged labor-inertia. The primary breech section rate for disproportion and inertia doubled in the past five years during which time there was a tremendous decrease in breech fetal mortality.

The comparison of the fetal mortality of cesarean section with that of vaginal delivery is impractical. The only fair comparison would be between entire groups of patients with similar pathology delivered by the two methods, rather than just the patient with the most serious complications being delivered by cesarean section, as is so often the case. Nevertheless, in this series there was no fetal mortality (corrected) in those cases of primary section for disproportion or for prolonged labor and/or uterine inertia, and only one fetal death (corrected) in the repeat disproportion group. Landesman[4] has pointed out that a section for cephalopelvic disproportion is of no more risk to the infant than spontaneous vertex delivery. The corrected fetal mortality for all term section babies (2,500 grams and over) was 1 per cent. The gross fetal mortality for all deliveries (vaginal and section) seven months and over was 3 per cent from 1940 to 1947, but reduced to 1.6 per cent from 1948 to 1952. In 1951 and 1952 the preventable term fetal loss for all deliveries was under 1 per cent.

While it is true that the cause of fetal death in most cases is inherent in the maternal complication which necessitate section, every effort should be made to avoid prematurity when possible, particularly in placenta previa, which has a 69 per cent section incidence. Prematurity exacts its toll! This study certainly emphasizes that fact. Nevertheless, prematurity cannot be helped in toxemia of pregnancy, which has a 10 per cent section incidence, due to the danger in continuation of the disease. The only answer here is prevention of toxemia, if possible.

Increased incidence of cesarean section in accidental hemorrhage, as well as earlier section in some cases, is advocated in the interest of fetal salvage. The section incidence of 18 per cent was increased to 30 per cent in 1952.

The use of sedation and/or general anesthesia undoubtedly increases fetal mortality. Pentothal Sodium may produce dangerous fetal asphyxia, and the obstetrician takes a *calculated risk* whenever he uses it. Spinal anesthesia has

been shown to be safe in our experience, but has its definite disadvantages and complications. Local Novocain is the safest anesthesia and probably should be used in most cases.

Full advantage should be taken of x-ray studies in the diagnosis and management of cephalopelvic disproportion. The obstetrician owes this much to his patient. X-ray is the most accurate and valuable method we have, but many obstetricians remain unconvinced.

Likewise, full advantage should be taken of trial and test of labor in indicated cases. Occasionally a mistake in judgment will result in the necessity for a difficult traumatizing forceps delivery unless the error is admitted, even after trial forceps, and a low flap section performed. In such a few instances the outcome has been good for both mother and baby.

I would like to suggest that we ought to stop applying the term "obstetric cripple" to the patient who has a cesarean section. Today, one routinely allows three cesareans (if low flap), and more can be done if particularly desired by the occasional patient. Then there is always the possibility of future vaginal delivery in many cases. I believe that it is entirely proper to state that most private patients can have all of the babies the family budget will allow, particularly in this day of planned pregnancies.

Unexplained fetal deaths will sometimes occur whether by vaginal delivery or by cesarean section. At the present time the hyaline-like membrane type of atelectasis apparently has to be expected occasionally, and seemingly more often in cesarean section than by vaginal delivery. It has been reported by Potter[17] that the incidence seems to be reduced by increasing the humidity in incubators where babies with respiratory distress are getting oxygen.

Today, maternal and fetal survival alone is not enough. The patient has the right to expect, under ordinary circumstances, that she will be fully restored to her former self, and without cystocele, rectocele, and prolapse in so far as our knowledge of their prevention goes; and that she will have a live and healthy baby. If cesarean section is elected, she has the right to expect that it will be performed before fetal damage takes place in so far as present knowledge will allow this decision to be made. In our present lack of knowledge concerning many problems, this decision cannot always be based upon absolute proof, or complete accuracy. There has to be some leeway, if we are to save babies. Moloy[6] has stressed the fact that we do not know the limits of safety of the squeeze effect of labor in disproportion. We can also say, for patients with bleeding, as in placenta previa and accidental hemorrhage, that we do not know the limits of safety for these babies.

Therefore, in conclusion, not only is it true, as Dieckmann has stated, that cesarean section is now a recognized procedure for the management of many obstetric and fetal complications formerly treated by vaginal delivery, but it is my opinion that cesarean section is the indicated procedure.

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Discussion

DR. HECTOR ROCAMORA (by invitation).—Our country, more and more influenced by the American School, departed many years ago from the classical practices, as will be demonstrated by the statistics to follow. First let me explain that the care given to our patients is somewhat different in this country than in the States. The private patients are sent to different centers (private institutions) than the ward patients who go to public hospitals. In the first instance the attention is personal; in the second instance the attention is given through a staff of interns and residents under our direction as professor of the University of Havana.

TABLE I. STATISTICS ON CESAREAN SECTION FROM THE WARD SERVICE, CALIXTO GARCIA HOSPITAL

YEAR	CASES	CESAREAN SECTION	PER CENT	MATERNAL MORTALITY		FETAL MORTALITY	
				NO.	%	NO.	%
1948	2,104	36	1.7	0	0.0	2	5.5
1949	1,953	49	2.5	0	0.0	2	4.0
1950	2,647	93	3.5	2	2.1	2	2.1
1951	3,074	85	2.7	1	1.1	2	2.3
1952	2 898	115	3.9	0	0.0	6	5.2
Total	12,676	378	2.9	3	0.7	14	3.7

TABLE II. STATISTICS ON CESAREAN SECTION FROM THE PRIVATE SERVICE OF THE MEDICAL CENTER

YEAR	CASES	CESAREAN SECTION		MATERNAL MORTALITY		FETAL MORTALITY	
		NO.	%	NO.	%	NO.	%
1948	226	11	4.8	0	0.0	0	0.0
1949	231	11	4.7	0	0.0	0	0.0
1950	267	14	5.2	0	0.0	0	0.0
1951	283	17	6.0	0	0.0	1	5.8
1952	306	23	7.5	0	0.0	0	0.0
Total	1,313	76	5.7	0	0.0	1	1.3

In both tables there is demonstrated the increased frequency of the cesarean operation from 4.8 per cent in 1948 to 7.5 per cent in 1952. We no longer use internal version, high forceps, or the difficult midforceps. When the head ceases to progress at the level of the sciatic spines we have substituted for the forceps two operations, namely, the cesarean section and the symphysiotomy. The latter is performed very seldom and only when the conditions of a given case are favorable, namely, with good uterine tone, well-molded head, and practically complete dilatation of the cervix. If these conditions are not present, we choose the abdominal route. This is the reason why during the year 1952 we performed only one symphysiotomy in our private patients.

The maternal mortality rate with the cesarean section is zero in private practice while it is 0.7 per cent in ward patients. There were three deaths on the ward service. One patient operated upon in very bad condition due to leukemia, died six days later. Pregnancy was interrupted in another patient in the eighth month because of pre-eclampsia, but notwithstanding this interruption, she had a convulsive seizure and twenty-four hours later she fell into a coma and died on the fourth postoperative day. The better results in private practice are due to the better preparation, attention, and study in this group.

We agree with Dr. Hunter Jones and others that the fetal mortality is due to the condition that calls for the operation and not to the operation itself. In our opinion the anoxia and prematurity are the principal causes of death. In our private practice during the last five years the only stillbirth was due to anoxia in a case of hemorrhagic placenta previa. Some of the principal indications for cesarean section are in the interest of the fetus.

The two most frequent indications for this operation are in the cases of cephalopelvic disproportion and those who have had previous sections. Then follow in order of frequency, uterine inertia and fetal distress. It is also true that the elderly primipara with or without previous infertility, the patient with a bad obstetrical history, and breech presentation are reasons for the growing number of cesarean sections. Hemorrhage due to placenta previa is perhaps the most precise indication. Exceptionally also we practice the cesarean section in cases of accidental hemorrhage and we sometimes interrupt the pregnancy in the pre-eclamptic stage of toxemia when it does not respond to medical treatment.

At the present moment we are of the opinion that in cases of previous section, it is a risk to permit trial of labor. Thanks to the low flap operation, we can give the patient the opportunity of having three children, which in the present condition of the world is more than sufficient.

In the primiparous women of our private practice we perform systematically Thoms' radiopelvimetric technique. In 90 per cent of the cases of cephalopelvic disproportion a trial of labor that lasts 6 to 8 hours is permitted. This is the length of time that we think is necessary.

For cesarean section we use the transperitoneal low flap technique, with a curved incision of the uterus. In most cases we follow the technique of Phannenstiel modified by Rodríguez López from Uruguay and B. Benach from Cuba. The use of extraperitoneal cesarean section in the private patient shows an inadequate obstetric conduct of the labor.

We prefer spinal anesthesia and only when there is a contraindication to this do we use cyclopropane-nitrous oxide and oxygen. We do not approve of the use of barbiturates, either as an anesthetic or as preanesthetic medication. We teach our patients throughout their pregnancies about the technique we are going to follow during delivery and if a natural way cannot be followed, we explain the operation to be performed.

We are living with a different kind of obstetrics. We have discontinued the internal version, the difficult forceps, and the traumatic delivery. They should occupy their places in the bookshelves of history. To this new obstetrics we have arrived step by step, not without hesitation and even with scruple, because when a cesarean section is indicated we think of the great number we have already performed.

Convinced by the results obtained in our long series of cesarean sections, and the low mortality of mother and baby, we nevertheless look back with respect to the old methods, yet we believe that we are on a safe path, and although we still feel the influence of the old school we do not regret the course we have been following.

DR. R. GORDON DOUGLAS, New York City.—I think it is very fitting that Dr. Jones has presented this timely paper on "The Trend in Cesarean Section in Recent Years" gained from experience in the Charlotte Memorial Hospital in Charlotte, N. C. Huber has recently stated that in the state of Indiana the incidence of cesarean section varies from 1 to approximately 20 per cent. This situation probably applies equally to other areas of this country. Obviously, some institutions have a section rate far in excess of what might be considered justifiable while, at the same time, it is likely that in others not enough sections are done. The essayist has pointed out that this rate on private patients is considerably greater than that for ward patients. Unfortunately, that same disparity exists in our own institution but apparently for a somewhat different reason than at the Charlotte Memorial Hospital. In our hospital the higher rate in private patients is due, to some extent, to the fact that more sections are done on a "repeat" indication on that service than on the ward service. I think the indications for cesarean section should be the same for both private and clinic patients. There must be an optimal incidence for this operation which should be alike for both services. In my opinion a rate in the neighborhood of 4 per cent in hospital practice probably represents the number of operations necessary to achieve the best results to both mother and baby. In a discussion such as this I must say that first consideration should be given to obtaining the best results. The actual incidence of the operation is of secondary importance.

I am personally not in accordance with the dictum "once a cesarean always a cesarean," and I am very happy to know that Dr. Jones feels much the same way. It is significant to note that the second maternal death recorded in this paper occurred in a 35-year-old woman who had a repeat cesarean section at 8½ months' gestation with a known small dead baby. I do not see how any one can help but attribute this death to the fact that a second cesarean section was done merely because the patient had been previously delivered that way. It is significant also to note that the writer reports one fetal death as a result of prematurity when obviously the elective section was done prior to the time the patient was at term. In all instances where a large series of elective cesarean sections are done prior to the onset of labor there will be a certain percentage where the babies are delivered prematurely and it appears reasonable, on the basis of experience, to anticipate a fetal mortality of 1 per cent for this reason. Accordingly, if a cesarean section is to be done this error can be obviated in all instances only by waiting for the onset of labor. By coincidence, during the meeting of this association in Florida two years ago a patient in the neighborhood who had been previously delivered by cesarean section commenced labor and during the proceedings of the meeting she was operated upon because she had had a previous cesarean section. The operation was completed but the patient died at the same time. I have no regrets concerning the policy that has been practiced for the last two decades in the New York Lying-In Hospital, that every patient be evaluated carefully as to indication for operation, and I do not believe that the history of a previous cesarean section alone warrants repetition of that procedure.

With respect to the type of operation done I am in complete agreement with the essayist that the low cervical cesarean section is the procedure of choice. While he reports almost an equal number of classical and low flap operations it is significant to note that their recent practice in the Charlotte Memorial Hospital very strongly favors the low segment procedure.

Dr. Jones has listed and very clearly stated his indications for operation. In general I am in agreement. However, I do not believe that cardiac disease per se constitutes a valid indication at any time for cesarean section. If the patient has an obstetrical indication for the operation all well and good but pregnancy complicating cardiac disease is much better terminated by birth through the normal passages. The author reports that 10 per cent of his operations were done for toxemia. This compares to a figure of about 4 per

cent on our service. Undoubtedly significant differences exist in the type and severity of toxemia encountered in Charlotte as compared to New York. It is difficult for me to believe that the procedure should be invoked as frequently, especially when the infant is under 1,500 grams, with the resultant high fetal mortality as reported by the essayist. Placenta previa seldom constitutes a surgical emergency. Conservative management in those patients with premature babies, until they are of term size, pays handsome dividends.

Dr. Jones has stated his experience with trial labors very well. A trial labor of 6 or 8 hours oftentimes gives very little added information. I am in complete agreement that a longer period of trial labor, without hour limitations, is frequently indicated and that sections based on short trial labors are often unnecessary. Under such circumstances patients can, and should, be adequately protected by the use of antimicrobial agents so that there will be no increased hazard of infection to the mother or to the baby.

If I understand the essayist entirely correctly, I do not believe that I can go along with everything he says concerning x-ray pelvimetry. I have known of too many unnecessary operations based entirely on the report of a roentgenologist in a general hospital who states that there is disproportion and that a cesarean section is indicated. To my way of thinking x-ray pelvimetry should be an aid to the clinician and used as any other diagnostic auxiliary service. I am a great believer in careful clinical evaluation of the pelvis; I am a firm believer in x-ray pelvimetry even to the extent of having all of the facilities for this procedure actually on our delivery floor. However, it is my distinct feeling that many unnecessary sections have been done merely because of an x-ray report in the record. An x-ray report should include facts concerning the pelvic architecture and size and any information that the roentgenologist cares to advance with respect to the size of the infant. But his report should conclude there. An expression of opinion as to the outcome of labor, as far as I am concerned, is beyond his prerogatives. I believe an obstetrician especially trained in x-ray techniques is the best qualified individual to interpret films and the more extensive the experience such people have the more they believe in these principles.

I find myself in complete agreement with the essayist in his philosophy concerning section and premature separation of the placenta. The same may be said of his management of breech presentation. I believe that his fetal mortality in toxemia of pregnancy is unusually high in that one-third of his babies died, the great majority from prematurity. I personally would feel that 18 sections where the infants were under 1,500 grams was probably in excess of what is actually necessary in the management of this complication. Dr. Jones' comments pertaining to Pentothal are very well made and, I am sure, completely justified. I do not like spinal anesthesia and do favor local, but we do not hesitate to use Pentothal for the actual delivery of the infant. This is usually commenced as the uterine incision is made. Using it in this fashion it is unlikely that any more than a mere trace of the barbiturate actually gets into the fetal blood stream.

Our experience is in conformity with that of Dr. Jones in that as our incidence of cesarean section has increased we have had a decrease in infant mortality. Obviously, many factors in addition to cesarean section are involved but a number of studies lend support to this statement. During the past two decades our incidence of cesarean section has increased from somewhat in excess of 2 per cent to over 4 per cent and during this period of time the over-all infant mortality has decreased from approximately 4½ to about 1½ per cent.

Undoubtedly significant trends include an increased role of this operation in diabetic patients, for premature separation of the placenta, placenta previa, and for fetal distress. Possibly the most important trend is the realization of the role of anesthesia which is as great a hazard as the operation itself. Any compromise of this principle with respect to agents or individual cannot be considered acceptable practice today.

PUERPERAL INVERSION OF THE UTERUS*

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THE recorded occurrence of puerperal inversion of the uterus is infrequent. This is due partly to its rarity; partly to its lack of recognition; and, undoubtedly, also, to the reluctance of some practitioners to risk liability.

Because of its rarity alone, it is reasonable to assume that no obstetrician will encounter a sufficient number of cases to arrive at logical conclusions concerning the variously advocated methods of treatment. Unfortunately, the available literature is conflicting in the variety of procedures and the contradictory steps recommended.

Our purpose here is to outline a clear course of procedure from an analysis of the data given in a number of cases. Certainly, sound reasoning dictates that opinions as to proper treatment be based on accumulated data.

Probodh Das,[1] in 1940, collected and critically analyzed 391 cases of inversion of the uterus, of which 297 were of the puerperal variety. Inasmuch as 1940 represents the time when whole blood transfusions were becoming more generally available and approximately dates the advent of modern chemotherapeutic and antibiotic therapy, it is felt that a review of the literature from 1940 to the present date will contribute additional information.

Definition

Inversion of the uterus means that the uterus is turned inside out. This catastrophe may occur during normal labor, abnormal labor, or in the nongravid uterus. Pedunculated myoma, carcinoma, or sarcoma may invoke the inversion of the nonpregnant uterus. Our primary concern in this investigation is the puerperal variety.

Kellogg[2] has suggested that the following classification is helpful for purposes of planning therapy:

A. Acute inversion: The acute catastrophe immediately following labor.

B. Subacute inversion: The stage beginning with the establishment of firm cervical contraction.

C. Chronic inversion: That stage beginning after the lapse of four weeks following known occurrence.

The terms complete and incomplete are sometimes used to indicate the proportion of the bulk of the uterus which has passed the external cervical os.[3]

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Etiology

Two conditions known to be necessary before inversion can occur are cervical dilatation and relaxation of a portion of the fundus of the uterus. Jones[4] and Phaneuf[5] liken any relaxed and indented portion of the fundus to a foreign body which the remainder of the uterus seizes and attempts to expel. The spontaneous inversion, according to Rankin,[6] is similar to the mechanism of intestinal intussusception.

Schaefer and Veprovski[7] outline the causes under the following headings:

A. Predisposing Causes
   1. Pathological conditions of the uterus and its contents.
   2. Functional conditions of the uterus.

B. Exciting Causes
   1. Manual removal of the placenta.
   2. Increase in intra-abdominal pressure.
   3. Mismanagement of the third stage of labor.

During the earlier part of this century, mismanagement of the third stage of labor generally was held responsible for most cases of inversion. Subsequently, the review by Das[1] indicates that 40 per cent were spontaneous in occurrence.

Diagnosis

The usually listed symptoms of acute inversion are shock, hemorrhage, pain, and mass in the vagina. These symptoms are so frequently absent that they cannot be depended upon to warn the physician of the accident. Any excessive blood loss should prompt immediate investigation. Shock is usually present and in this case is usually out of proportion to the blood loss. Dimpling or cupping of the fundus, when present, is an extremely valuable sign. Spain[8] states that cupping is so infrequently recognized that its apparent absence is of no diagnostic value. Complete absence of the palpable fundus is a valuable sign when present. The condition should be immediately recognized when the mass of the inverted fundus passes the vulva.

However, the detection of this condition can be insured. Kaltreider and West[9] state that routine cervical inspection, besides demonstrating trailing membranes and cervical lacerations, will always reveal the presence of inversion. Routine immediate puerperal vaginal examination will demonstrate the presence of the inverted fundus.

Treatment

The multitude of available therapeutic methods attests to the inadequacy of any one method in all cases. Manual replacement has been used more widely than any other single method. It is strongly recommended by Cosgrove,[10] Barrett,[11] and others. McLennan and McKelvey[12] advocate conservative treatment, with immediate aggressive shock therapy, followed by correction of the inversion by surgical methods at a later date. Nugent and

MacKinnon[13] also recommend that immediate manual reposition never be attempted because of the shock that is usually produced. O'Sullivan[14] describes the procedure of reducing the inverted uterus with the use of intravaginal hydraulic pressure made by giving a douche with the introitus closed. Clahr and Wurzbach[15] reduced the inverted fundus by overdistention of the vagina with tight packing. Aveling's repositor has been used successfully.

The operative techniques of Spinelli, Huntington, and also of Haultain[16] are specifically designed for treatment of puerperal inversion. Abdominal and vaginal hysterectomy have both been employed.

Material

Our analyses have been drawn from certain literature and from limited personal observation.

A. We have reviewed the American and English literature from 1940 to mid-1952:

1. To determine if the more ready availability of whole blood and the use of antibiotic drugs has changed the prognosis in puerperal inversion.
2. To compare the mortality during the past decade with previous results as summarized by Das.[1]
3. To rationalize a plan of therapy dependent upon the time of recognition of the inversion.

Unfortunately, we find that the date of occurrence of inversions is frequently omitted from the written reports. We have assumed many to have occurred since 1940 because antibiotic drugs were given. Some included cases could have happened prior to 1940. Tables I to VI present the cases reviewed.

B. We add two personal cases.

CASE 1.—Roper Hospital No. A-5917. A 21-year-old gravida iv, para ii, abortus i, had her last regular menstrual flow Feb. 20, 1951. The prenatal course was uncomplicated to Sept. 7, 1951, when the membranes ruptured spontaneously. On admission four hours after rupture, she was in active labor. The fetal heartbeat was never heard. Labor was desultory with weak, irregular contractions throughout. Spontaneous delivery of a stillborn infant that weighed 1,800 grams occurred twenty-one hours after the onset of labor. The placenta separated five minutes after delivery and was delivered easily with the modified Credé maneuver. Two minutes after delivery of the placenta, vaginal bleeding became quite brisk. The fundus was indistinctly palpable above the symphysis. Immediate vaginal examination revealed the fundus to lie in the vagina, protruding through a distinctly palpable cervical ring. Shock was not evident. The fundus was immediately replaced by gentle pressure with the palm, while the fingers retracted the cervical ring. Ergot was given intravenously, the fundus contracted well, and the excessive bleeding stopped abruptly. The puerperium was not morbid.

No cause for the stillbirth was demonstrable. The uterus was well involuted at the time of postpartum examination.

CASE 2.—Baker Sanatorium No. 53721. A 22-year-old white gravida i, para 0, was admitted at term in early labor on Jan. 26, 1951. After ten hours of progressive labor, she was delivered of a living female infant that weighed 3,270 grams. Outlet forceps were used. The placenta was delivered eleven minutes later. Moderate traction was applied to the cord at the time of delivery.

Following the completion of the third stage of labor, there was profuse vaginal bleeding. The patient immediately was deeply shocked. Immediate vaginal examination

TABLE I. CASES IN WHICH PATIENT DIED BEFORE TREATMENT

AUTHOR	AGE (YEARS)	PARITY	DELIVERY	PLACENTA	SYMPTOMS	RECOGNITION	TREATMENT	RESULT
Torpin[17]	16	i	Spont.		Hemorrhage and shock	2 days	None	Died
Torpin[17]							None	Died
Thomas[18]			Forceps	Pressure	Hemorrhage and shock	66 minutes	None	Died
Long[19]	19	ii	Spont.	Credé	Hemorrhage and shock	Immediate	None (at home)	Died 76 minutes
Benson[20]	20	i				At necropsy	None	Died

TABLE II. CASES DISCOVERED DURING FIRST THIRTY MINUTES TREATED BY MANUAL REPOSITION

AUTHOR	AGE (YEARS)	PARITY	DELIVERY	PLACENTA	SYMPTOMS	RECOGNITION	TREATMENT	RESULT
Kaltreider[9]	23	i	Forceps	Credé	Visible	Immediate	Immed. man. repos.	Recovered
Kaltreider[9]	24	ii	Forceps	Credé	Visible	Immediate	Immed. man. repos.	Recovered
Kaltreider[9]	18	i	Forceps	Credé	None	Immediate	Immed. man. repos.	Recovered
Kaltreider[9]	19	i	Forceps	Credé	Hemorrhage	Immediate	Immed. man. repos.	Recovered
Torpin[17]	22	i	Spont.	Spont.	Visible	Immediate	Immed. man. repos.	Recovered
Torpin[17]	40	x	Spont.	Traction	Hemorrhage and shock	Soon	Immed. man. repos.	Recovered
Torpin[17]	38	ii	Spont.	Traction	Visible	Immediate	Immed. man. repos.	Recovered
Torpin[17]	21	i	Spont.	Spont.	Visible	Immediate	Immed. man. repos.	Recovered
Torpin[17]	29	i	Forceps	Traction	Visible	Immediate	Immed. man. repos.	Recovered
Torpin[17]	24	i	Spont.	Spont.	Hemorrhage and shock	30 minutes	Immed. man. repos.	Recovered
Fenton[21]	19	i	Forceps	Credé	Visible	Immediate	Immed. man. repos.	Recovered
Fenton[21]	25	i	Forceps	Credé	Visible	Immediate	Immed. man. repos.	Recovered
Fenton[21]	23	ii	Spont.	Spont.	Hemorrhage	Soon	Immed. man. repos.	Recovered
Donaldson[22]	34	iv	Spont.	Spont.	Pain*	10 minutes	Immed. man. repos.	Recovered
Johnson[23]	30	ii	Spont.	Credé	Shock	Immediate	Immed. man. repos.	Recovered
Hendricks[24]	21	i	Spont.	Spont.	Shock	Immediate	Immed. man. repos.	Recovered
Spain[8]	34	iii	Spont.	Spont.	Hemorrhage and shock	10 minutes	Immed. man. repos.	Recovered
Burwig[25]	23	i	Forceps	Spont.	Visible	Immediate	Immed. man. repos.	Recovered
Sussman[26]	24	i	Forceps	Credé	Visible	Immediate	Immed. man. repos.	Recovered
Chisholm[27]	22	i	Spont.	Spont.	Shock	Immediate	Immed. man. repos.	Death†

*Two and one-half hours later while voiding.
†Shock.

TABLE III. CASES DISCOVERED AFTER THIRTY MINUTES AND TREATED IMMEDIATELY BY MANUAL REPOSITION

AUTHOR	AGE (YEARS)	PARITY	DELIVERY	PLACENTA	SYMPTOMS	RECOGNITION	TREATMENT	RESULT
Spain[8]	22	iii	Spont.	Manual	Hemorrhage and shock	45 minutes	Immed. man. repos.	Died*
Kaltreider[9]	25	ii	Spont.		Hemorrhage	6 hours	Immed. man. repos.	Recovered
Kaltreider[9]	25	i	Spont.	Credé	Hemorrhage and shock	4½ hours	Immed. man. repos.	Died†
Torpin[17]		ii	Breech	Traction			Man. repos.	Died‡
Johnson[23]	23	i	Breech	Spont.	Hemorrhage and shock	2 months	Immed. man. repos.	Recovered
Johnson[23]	28	ii	Forceps	Difficult	Hemorrhage and shock	7 hours	Immed. man. repos.	Recovered
Johnson[23]	26	ii	Spont.		Hemorrhage	3 months	Immed. man. repos.	Recovered
Johnson[23]	23	i	Forceps		Hemorrhage and shock	7 hours	Immed. man. repos.	Recovered
Johnson[23]	28	i	Forceps		Hemorrhage and shock	2½ hours	Immed. man. repos.	Recovered
Johnson[23]	29		Forceps		Hemorrhage and shock	3 hours	Immed. man. repos.	Recovered
Allen[28]	28	ii	Spont.	Traction	Hemorrhage and shock	3 hours	Immed. man. repos.	Recovered

*On the tenth day of anterior pituitary necrosis.
†Shock.
‡Infection.

TABLE IV. CASES TREATED BY UNUSUAL METHODS

AUTHOR	AGE (YEARS)	PARITY	DELIVERY	PLACENTA	SYMPTOMS	RECOGNITION	TREATMENT	RESULT
Schaefer[7]	29	iii	Spont.		Hemorrhage and shock	Immediate	Man. repos. failed Pack corrected invers.	Recovered
Kaltreider[9]	26	i	Spont.	Traumatic	Hemorrhage and shock	3½ hours	Pack corrected invers.	Died*
O'Sullivan[14]	24	iii	Breech	Expression	Hemorrhage and shock	45 minutes	Repair of uterus, then hydraulic douche	Recovered
O'Sullivan[14]	31	ii	Spont.	Credé	Hemorrhage and shock	Immediate	Hydraulic douche	Recovered
O'Sullivan[14]	21	ii	Spont.	Manual	Hemorrhage and shock	1 hour	Aveling's repositor Thirty-fourth day	Recovered
Clahr[15]	23	ii	Spont.	Spont.	Hemorrhage and shock	45 minutes	Vaginal pack	Recovered
Loizeaux[40]	19	i	Forceps	Spont.	Hemorrhage and shock	2½ hours	Man. repos., then tight packing for 15 days	Recovered

*Shock irreversible.

TABLE V. CASES OF FAILED OR DELAYED MANUAL REPOSITION

AUTHOR	AGE (YEARS)	PARITY	DELIVERY	PLACENTA	SYMPTOMS	RECOGNITION	TREATMENT	RESULT
Schaefer[7]	21	i	Forceps	Spont.	Hemorrhage and shock	Immediate	Man. repos. failed*	Recovered
McLennan[12]	22	i	Forceps	Spont.	Hemorrhage and shock	30 minutes	Man. repos. failed	Died†
Nugent[13]		i	Forceps	Traction	Visible	Immediate	Attempt man. repos. caused shock. *Man. repos. 16 hours	Recovered
Torpin[17]	16	i	Spont.	Manual	Hemorrhage	4 days	Man. repos. 8 days	Recovered
Benson[20]	26	iii	Spont.	Spont.	Visible	Immediate	*Man. repos. 4 days	Recovered
Johnson[23]	25	i	Forceps	Credé	Hemorrhage and shock	Immediate	*Man. repos. 1 hour	Recovered
Johnson[23]	19	i	Forceps	Credé	Hemorrhage and shock	12 hours	Man. repos. failed *Man. repos. 14 days	Recovered
Burwig[25]	20	iii	Spont.	Credé	Hemorrhage and shock	Immediate	*Man. repos. 6 days	Recovered
Burwig[25]		ii	Forceps	Credé	Hemorrhage and shock	Immediate	*Man. repos. 7 days	Recovered
Burwig[25]	28	i	Spont.	Credé	Hemorrhage and shock	8 hours	*Man. repos. 6 days	Recovered
Allen[28]	31	ii	Spont.	Credé	Hemorrhage and shock	1 hour	*Man. repos. 2 hours	Recovered
Mendoza[29]	35	vii	Spont.	Spont.	Mass	3½ hours	Man. repos. 19 hours	Recovered
Patton[30]	17	i	Forceps	Spont.	Hemorrhage and shock	12 minutes	Man. repos. 45 minutes	Recovered
Patton[30]	26	iii	Spont.	Credé	Hemorrhage and shock	66 minutes	Man. repos. in shock 54 minutes later	Died†
Allen[28]	21	i	Spont.	Expressed	Hemorrhage and shock	Immediate	Man. repos. failed Effort repeated 1½ hours	Died†

*Shock treated.
†Died in shock.

TABLE VI. CASES TREATED SURGICALLY

AUTHOR	AGE (YEARS)	PARITY	DELIVERY	PLACENTA	SYMPTOMS	RECOGNITION	TREATMENT	RESULT
Schaefer[7]	26	ii	Forceps	Pressure	Hemorrhage and shock	Immediate	Man. repos. 3 days. Recurred. Spinelli 66 days	Recovered
McKeown[6]	17	i	Spont.	Spont.	Mass 13 days	13 days	Spinelli 28 days	Recovered
Kaltreider[9]	26	ii	Forceps	Credé	Hemorrhage and shock	Immediate	Man. repos. failed Huntington 1½ hours	Recovered
McLennan[12]	31	i	Forceps	Traction	Hemorrhage and shock	1 month	Abdominal replacement	Recovered
McLennan[12]	26	ii	Spont.	Credé	Hemorrhage and shock	4 hours	Vaginal hysterectomy 10 weeks	Recovered
Torpin[17]		i	Spont.	Manual	Hemorrhage and shock		Haultain 3½ weeks	Recovered
Torpin[17]	26	i	Spont.	Spont.	Hemorrhage and shock	Immediate	Packed. Spinelli 3 weeks later	Recovered
Torpin[17] *			Spont.	Massage	Hemorrhage and shock	Soon	Man. repos. failed Operation 2 weeks	Recovered
Benson[20]	39	iii	Spont.		Fever 4 days	96 days	Uterus removed	Recovered
Bigby[31]		ii	Spont.	Credé	Hemorrhage and shock		Man. repos. failed 2½ hours. Huntington 6½ hours	Recovered
Reid[32]	24	i	Spont.	Expelled	Hemorrhage and shock	7 hours	Huntington 9 hours	Died†
Mundt[33]	20	i	Spont.		Urinary retention	3 days	Vaginal hysterectomy 7 days	Recovered
Johnston[34]	18	i	Spont.	Spont.	Hemorrhage and shock	2½ hours	Man. repos. failed. Huntington 4 hours	Recovered
Shragg[35]	35	iii	Breech	Spont.	Hemorrhage and shock	Immediate	Abdominal hysterectomy 6 hours	Recovered
O'Connor[36]	22	i	Forceps	Spont.	Hemorrhage and sepsis	25 days	Vaginal hysterectomy 25 days	Recovered
Kobak[37]	22	i	Forceps	Credé	Hemorrhage and sepsis	5 days	Abdominal hysterectomy 47 days	Recovered
Hart[38]	18	i	Breech	Spont.	Hemorrhage and shock	Immediate	Partial repos. Immediately. Hysterectomy 24 days	Recovered
Salvin[39]		i	Breech	Spont.	Hemorrhage	Immediate	Man. repos. Recurred 23 days. Hysterectomy	Recovered

*Recurrence preceding case 1½ years later.
†Death followed surgery by two days.

revealed the mass of the inverted fundus lying in the vagina. Gentle pressure did not replace the fundus. The vagina was packed and shock therapy was instituted. Fifteen hundred c.c. of whole blood was given through multiple sites. Shock was adequately controlled. At two and one-half hours post partum, under general anesthesia, the mass of the inverted fundus was replaced manually.

The puerperium was uncomplicated. On Nov. 23, 1952, this patient delivered her second infant without mishap.

Comment on Reviewed Literature

1. In the 67 cases where the age was stated, the average age was 24.5 years. The youngest patient was 16 years old. The oldest patient was 40 years old. Das' review indicated that 53.6 per cent of the cases occurred between the ages of 21 and 30 years. Sixty-five and eight-tenths per cent of the present group were between 21 and 30 years old. Table VII indicates the age distribution.

TABLE VII. AGE INCIDENCE OF PATIENTS WITH PUERPERAL INVERSION OF THE UTERUS

AGE (YEARS)	NO. OF PATIENTS	PERCENTAGE
Under 20	12	17.9
20-24	25	37.5
25-29	19	28.3
30-34	6	8.9
35-40	5	7.4
Total	67	100.0

2. Parity was stated in 73 of the 76 cases reviewed. Das' review indicated that 52 per cent of the cases occurred in primiparas. Table VIII outlines parity in the current review.

TABLE VIII. PARITY OF PATIENTS WITH PUERPERAL INVERSION OF THE UTERUS

PARITY	NO. OF PATIENTS	PERCENTAGE
i	43	58.9
ii	18	24.7
iii	9	12.3
iv or more	3	4.1
Total	73	100.0

3. The local incidence of puerperal inversion of the uterus was stated in reports representing only 30 of the 78 currently analyzed cases. From these reports, the incidence is calculated to be one in 4,894 deliveries. This is approximately three times the incidence of one in 14,881 deliveries as calculated by Das.[1] The incidence of inversion on the obstetrical service of Roper Hospital during the past 12 years is one case in 23,221 deliveries.

4. The method of delivery could not in any way be correlated with the occurrence of puerperal inversion. Mismanagement of the third stage of labor was difficult to evaluate because of the brevity of most reports. The inversion occurred spontaneously in 38 per cent of the cases reviewed, which parallels very closely the 40 per cent as calculated by Das.[1]

5. Hemorrhage was the most frequently encountered single symptom of acute inversion, being present in 68 per cent of the cases. Surprisingly, shock was present in only 63 per cent of this group of cases. In 21 per cent the inversion was directly recognized by the presence of a visible uterine mass at the vulva. Urinary retention, fullness of the vagina, and postcoital bleeding were the least frequent symptoms. Apparently, in no case did the recognition of a fundic dimple alone lead directly to the recognition of the inversion.

6. Time of recognition of the inversion varied widely between the extremes of immediate recognition to discovery 96 days later at the time of postpartum examination. Table IX lists the time of recognition with the additional factor of maternal mortality calculated in each group.

TABLE IX. TIME OF RECOGNITION OF INVERSION

TIME	NO. OF CASES	NO. OF DEATHS	PERCENTAGE
0-30 minutes	42	4	9.5
30-60 minutes	4	1	25.0
1-24 hours	17	5	29.2
24-48 hours	4	4	100.0
Over 48 hours	9	0	0.0

It appears from these figures that immediate recognition offers the best chance of survival, irrespective of the type of treatment given. The mortality seems to rise steadily as recognition is delayed up to the point of about 48 hours. If the patient with unrecognized inversion survives beyond 48 hours, the mortality declines very sharply.

7. Five patients received neither treatment for hemorrhage and shock, nor definitive treatment of the inversion. These patients usually arrived at the hospital in a moribund condition and died before recognition or the institution of therapy.

Twenty cases were discovered within 30 minutes and treated immediately by manual reposition. In this group of 20 cases there was only one death. This patient suffered deep shock with no hemorrhage immediately after reposition and died soon after the procedure.

Eleven cases discovered between 30 minutes and three months of the puerperal inversion were immediately treated successfully by manual reposition. Of these 11, 3 patients died.

Thirteen patients, all demonstrating evidence of hemorrhage or shock, received immediate shock therapy upon discovery of the inversion. After the shock was treated, the inversion was corrected by manual reposition. Of this group, only one patient died. She died of shock one hour after completion of the replacement.

Two patients had vigorous unsuccessful attempts at manual replacement while in deep shock. Both of these died of shock.

Eighteen patients were treated by a variety of surgical procedures. Seventeen of these patients had active shock therapy during the acute phase of the

inversion. Six of these experienced unsuccessful attempts at gentle manual reposition. One patient in this group died two days after the Huntington operation.

Seven cases were treated variously as listed in Table X.

TABLE X. METHODS OF TREATMENT

METHOD OF TREATMENT	NO. OF CASES	NO. OF DEATHS	PERCENTAGE
Immediate reposition first 30 minutes	20	1	5.0
Immediate reposition upon discovery but later than 30 minutes	11	3	27.2
Shock treatment, then reposition	13	1	7.7
Vigorous attempts at reposition	2	2	100.0
Operative treatment after shock therapy	18	1	5.5
Hydraulic douche	2	0	0.0
Aveling's repositor	1	0	0.0
Tight vaginal packing	4	1	25.0

Of the 78 cases reviewed, 14 patients died. This gives an uncorrected maternal mortality of 17.9 per cent. However, of the 14 patients who died, only 9 were recognized to have inversion and received active treatment in any form. Considering only the recognized and treated patients, the mortality is 12.3 per cent.

Conclusions

1. The maternal mortality from puerperal inversion of the uterus has not been reduced markedly during the past 12 years even though whole blood transfusions and antibiotic drugs have been more readily available.

2. Review of the literature for the past 12 years shows the uncorrected mortality to be 17.9 per cent. Considering only the patients who received treatment, the mortality was 12.3 per cent. Das' review indicated the mortality to be 13.2 per cent.

3. Delay or failure of recognition seems to be the greatest impediment to further reduction of mortality from puerperal inversion.

4. From the results obtained in the cases reviewed, the following plan of therapy emerges:

a. Anticipation of inversion and more judicious management of the third stage of labor can lower the incidence.

b. Recognition of inversion can always be ensured by making cervical inspection or immediate puerperal vaginal examination a routine procedure.

c. In cases recognized during the first 30 minutes post partum, and before tight cervical contraction, manual replacement should be done immediately. Shock therapy should be started simultaneously.

d. In the absence of hemorrhage and shock, in cases recognized before cervical contraction, manual replacement should be done immediately regardless of the time elapsed since occurrence.

e. After the lapse of about 30 minutes, which usually marks the beginning of cervical contraction, treatment should be directed toward correction of blood loss and shock. After shock is corrected, an attempt at gentle manual replace-

ment should be made. If tight cervical contraction precludes easy manual replacement, operative replacement should be done. The Huntington procedure should be satisfactory during the subacute stage.

f. Chronic inversion can be treated by manual reposition in some cases. Operative replacement by the Spinelli procedure is satisfactory when manual replacement fails.

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Discussion

DR. H. HUDNALL WARE, JR., Richmond, Va.—The review of Dr. Bell and Dr. Wilson of the American and English literature from 1950 to mid 1952 brings together for analysis the reported cases of puerperal inversion of the uterus and reveals some important statistical evidence concerning the treatment of this rare complication.

McCullagh, according to Eastman, estimates that puerperal inversion of the uterus occurs once in 30,000 labors and, at Johns Hopkins Hospital, it occurred once in the last 20,000 deliveries. Cosgrove says that in 20,000 living births from 1913 to 1931 no inversion of the uterus occurred on his service, but in the seven-year period prior to 1939 nine cases occurred on his service with less than twice as many births as in the previous period.

It seems evident that some patients develop puerperal inversion of the uterus without mismanagement of the third stage of labor. It also seems evident that inversion of

the uterus frequently results from mismanagement of the third stage of labor, particularly from traction on the umbilical cord, which I think should be consistently avoided. The clamped cord should be placed on the abdomen just above the symphysis until the placenta has been expelled from the vagina. Any traction on the cord may be more forceful than the operator realizes.

Drs. Bell and Wilson have reviewed the methods most frequently advocated for treatment of inversion of the uterus and I concur with them that immediate vaginal examination or inspection of the cervix after delivery will enable the attendant to diagnose inversion of the uterus. From the collected reports, it is evident that immediate recognition of inversion of the uterus enables the operator to replace the inverted uterus manually and treat the shock that is sometimes associated with inversion of the uterus.

I wish to report two new cases of puerperal inversion of the uterus. The first occurred in my private practice and it is the only case of puerperal inversion of the uterus I have actually seen occur. The placenta was separated immediately from its attachment in the fundus of the uterus and the inversion was corrected by taxis within two minutes after it occurred. The total blood lost during the delivery was less than 200 c.c. and the patient showed no change in pulse rate or blood pressure.

CASE 1.—A. H. A., white, gravida i, aged 24 years, was a private patient whose prenatal course was normal until Oct. 29, 1941, when her blood pressure was elevated to systolic 140 and diastolic 90 and she was admitted to the Medical College of Virginia Hospital for observation. She was thirty-eight weeks pregnant. On November 1, three days after admission to the hospital, labor was induced with castor oil. The labor was uneventful and after fourteen hours the fetal head showed at the vulva in a vertex right occipitoposterior position. The patient was given nitrous oxide, oxygen, and ether anesthesia, a median episiotomy was done, the fetal head was easily rotated manually to right occipitoanterior position and delivered with low forceps. The baby, a female, weighed 6 pounds, 13 ounces (3,090 grams). She breathed and cried immediately and remained in good condition. The clamped end of the umbilical cord was placed on the patient's abdomen just above the symphysis and the uterus was held gently. Twenty minutes after delivery the placenta was expressed by Credé's maneuver. The uterus had inverted and the placenta was attached in the fundus. It was quickly peeled off from the uterus and the inversion corrected by pressure in the fundus of the uterus. There was no free bleeding and the uterus was packed with two strips of three-inch packing. The patient lost less than 200 c.c. of blood during the delivery and treatment of the inversion. Her pulse and blood pressure showed no change and her condition remained good. The uterine packing was removed after twenty-four hours. There was a slight elevation of temperature in the afternoon for three days, but her convalescence was otherwise normal. Her condition remained good and her pelvic structures were normal when she was last seen one year after delivery.

CASE 2.—E. T., B-09-57-29, Negro, aged 35 years, gravida vi, para iv, abortions i, was admitted to the ward obstetrical service, St. Philip Hospital, Dec. 31, 1952, at 8 P.M. because of a uterine pregnancy of five months' duration complicated by spontaneous premature rupture of the membranes and premature labor. Her last regular menstrual period occurred July 18, 1952.

The pregnancy had been uneventful until November 15 when she experienced some severe periumbilical cramping sensations for three hours. She was then well until Dec. 4, 1952, when the membranes ruptured spontaneously at home and she passed small quantities of amniotic fluid. She had noticed occasional uterine contractions which had increased in severity for three weeks prior to admission to the hospital. She noticed chilly sensations the day before entering the hospital and had a severe chill which lasted thirty minutes just before admission. Her family stated that each chill was followed by an emotional upset and the patient screamed and seemed exhausted.

She has four living children, aged 9, 12, 14, and 15 years, respectively. Her last pregnancy occurred in 1950 and terminated as a spontaneous abortion at the third month

of pregnancy. The abortion was associated with severe hemorrhage, the uterus was curetted, and she received six whole blood transfusions, a total of 3,000 c.c.

On admission, Dec. 31, 1952, her temperature was 102° F. orally. Blood pressure was systolic 110 and diastolic 60, pulse 90, respirations 14. Hemoglobin was 9.2 Gm., Wassermann test negative. Urine showed a specific gravity of 1.003 and was otherwise normal. Examination revealed a pelvic and abdominal tumor compatible with a six months' pregnancy and uterine contractions were occurring every five minutes. Fetal heart sounds were heard in the right lower quadrant, rate 150 per minute. She was treated with Crysticillin and Gantrisin.

After twenty-four hours her temperature was 100° F. orally. The patient was extremely tender over the lower abdomen and the uterus was firmly contracted. She was given streptomycin and Crysticillin was continued. On January 1, around midnight, she was seen by an intern who thought she was ready to deliver. She complained of a chilly sensation, was slightly cyanotic, and her blood pressure could not be obtained.

She was moved to the delivery table and fifteen minutes later delivered as a compound presentation a deadborn fetus that weighed 1,490 grams. The head presented with a hand prolapsed to the level of the vertex and both legs were around the neck of the fetus. Following expulsion of the fetus, the patient bled profusely for a few seconds and the intern estimated that she lost 300 c.c. of blood. She was still in shock and her blood pressure could not be obtained. An attempt was made to express the placenta by pressure on the fundus of the uterus. The uterus inverted with the placenta attached. A resident was called and within ten minutes the placenta was peeled off with ease and the uterus replaced manually by pressure in the fundus. Examination of the uterus by the resident revealed an extensive rupture in the left side below the cornu. With his hand covering the tear in the uterine wall, the uterine cavity was packed with gauze. The fundus of the uterus contracted firmly and the patient's blood pressure was then obtained. A transfusion with whole blood was started and intravenous glucose solution was also given. The patient was moved to the operating room and a supracervical hysterectomy was done under cyclopropane anesthesia. During the operation the patient's blood pressure gradually increased from systolic 60 and diastolic 30 to systolic 90 and diastolic 60. At the beginning of the operation her pulse was 160 and it decreased to 120. She received a total of 6,500 c.c. of whole blood and it was estimated she lost 6,000 c.c. of blood. Four hours after the operation her blood pressure was systolic 110 and diastolic 86, pulse 120, and she was alert and rational.

On Jan. 3, 1953, her hemoglobin was 16.6 Gm. and the blood pressure, systolic 115 and diastolic 80. She was alert and rational. The patient's temperature was 103.8° F. at one reading the day of operation. Then it remained below 100 degrees until the fifth day after operation when at one reading it was 100.6°. Again on the sixth and seventh days after operation it was above 100° for one reading each day. Then it remained 100° or below. The abdominal incision healed, but she developed a psychosis which commenced on the third postoperative day and she was transferred to a hospital for mental patients on Jan. 14, 1953.

The last case presents many problems. She was probably mentally upset before admission to the hospital and it is difficult to determine whether the spells she had were due to pain or a mental illness. The intern who attended this case does not think the inversion was caused by his attempts to express the placenta. The resident removed the placenta easily and thinks the rupture of the uterus occurred before the inversion.

Can one reduce the hemorrhage associated with a rupture in the uterine wall by packing the uterus immediately and remove the packing when the operator is ready to remove the uterus by abdominal operation? In selected cases, properly packed, I think we can reduce the blood loss.

What part did the anoxia associated with shock contribute to the patient's mental illness? This is difficult to determine; the patient was certainly mentally upset when she was admitted to the hospital, but she was mentally alert and cooperative for four days after the operation.

DR. EMILIO YERO BOU, Havana, Cuba (by invitation).—It is our opinion, too, that uterine inversion is a rare accident, for at our Maternity Hospital we have found it only twice in approximately 40,000 labors. It has been attributed frequently to defective technique, but we believe that, besides, it is necessary that certain anatomic conditions exist, predisposing to its production.

Its treatment is, of course, when possible, immediate reduction of the inversion, taking advantage of the same flaccidity of the uterus that has made the accident possible. But when a state of shock has been established, and a strong uterine or cervical retraction exists, I am opposed to any handling of the organ whatsoever, believing that this may aggravate the shock and rapidly lead to the death of the patient.

Therefore, we think that the treatment of the state of shock is necessary before all else. Once the patient has reached a chronic state she may be treated so as to improve her general condition till it is favorable for operation.

The procedure actually most widely used among us for the solution of these cases in their chronic state is the original one of our colleague, Dr. Julián Ocejo, who called it anterior abdominal vaginocervical hysterotomy. The technique, as described by him, is very easy. The abdomen is opened and the constricting ring is raised with two Allis clamps. With a knife, the vesicouterine peritoneum is cut from one round ligament to the other. The peritoneum is thereby freed from the anterior wall of the vagina, as in Wertheim's panhysterectomy. Scissors are introduced into the fundus and the cervix and adjacent portion of the vagina and the body are divided longitudinally in the midline. The finger is introduced into the fundus and the body of the uterus is pulled into the abdomen. After the corpus has been replaced, reinversion of the uterus is done with the fingers. The cervix is sutured first, then the body, and last of all, the vagina. The entire surface denuded is covered with the vesicouterine peritoneum. A round ligament suspension completes the procedure.

SYMPHYSIOTOMY VERSUS DIFFICULT FORCEPS*

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WE USUALLY divide forceps operations into three classes: high forceps, medium forceps, and low forceps. High forceps have practically disappeared from obstetrical practice. Indeed, I think I have never really performed a high forceps application. Such cases can be recognized early enough to perform cesarean section without any anxiety. At the other extreme, episiotomy and low forceps, the prophylactic forceps of DeLee, have become almost a part of normal delivery.

Conditions are not so easy when the fetal head meets with some interference around the spines. Most of these cases are occiput posterior or transverse presentations with an incompletely flexed vertex. The complete prevention of such a condition must be regarded as very difficult. Prenatal care, accurate x-ray pelvimetry with special emphasis on midplane dystocia, careful attention during labor, and the wider use of cesarean section have reduced midplane dystocia to a condition of some rarity. Notwithstanding all this, what obstetrician can be sure he will never have to face a case of midplane dystocia?

In such cases, cervical dilatation is complete or nearly so, the membranes have been ruptured for many hours, uterine contractions are absolutely normal and cooperation from the patient is perfect. In spite of all that, there is an arrest of the head at the level of the spines. The time elapsed and the internal examination during the uterine contractions demonstrate the arrest. Every obstetrician when facing this situation will agree that, could a little more room be obtained within the pelvis, the condition would be overcome. However, midplane dystocia is usually solved by means of medium forceps. The results have not been too good.

Naturally, I am aware that cesarean section can be done in such cases, but I myself would feel that I was lacking a valuable technique were I unable to obtain a little more room inside the pelvis when necessary. My presence here may be justified if I succeed in proving that, in case of midplane dystocia, the section of the symphysis is much better for mother and child than the medium forceps operation.

I well know your prejudice against symphysiotomy and you are partly justified, because what you may have heard is the sad history of cases done under wrong diagnosis and indications, with poor technique and improper aftercare. I also know that the case does not end with symphysiotomy. There

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is always a delivery afterward. Early ambulation is impossible. After 48 hours, the patient starts exercises in bed and only when all horizontal exercises can be done without any pain is the patient allowed to get up and leave the bed. This usually happens about two weeks after symphysiotomy and means that the mother needs a real period of time for recovery after this operation. Yet in a few weeks at the most that recovery is complete, whereas the brain injuries of many midforceps babies are permanent.

Technique of the Operation

The best anesthesia is saddle block with Heavy Nupercaine. The patient is placed in the obstetrical position and the usual aseptic preparation carried out. A rubber catheter is inserted in the bladder. The index and middle fingers of the left hand are placed in the vagina against the posterior aspect of the symphysis, displacing the urethra with the rubber catheter from the midline. The fingers in the vagina locate the upper border of the symphysis. An ordinary laparotomy knife, not too wide, is introduced through the skin and the fat over the middle part of the symphysis and then carried, always under the skin and fat, to the upper part of the symphysis where it makes a small opening and starts the downward section of the symphysis. At that moment we change the usual laparotomy knife for a protected knife, really a strong tenotome, with which we have to cut only the ligaments that form the articular capsule of the symphysis. The vaginal fingers guide the protected knife which cuts the upper articular ligament, the posterior, most of the fibers of the anterior, and finally the arcuate ligament.

The symphysis spreads gradually. We never need more than one finger-width or a little more of separation between the pubic bones. At this point one may note two bridges of firm tissue, one immediately over the symphysis, the other immediately underneath. These hold the pubic bones together, preventing a wider separation and are like the ligaments of an opened articulation. Both bridges are formed of strong connective tissue, the upper by the insertion of the tendons of the recti, oblique, and pyramidalis muscles. The lower bridge is the preurethral ligament, a part of the middle perineal fascia.

If there is any bleeding through the opening in the skin, a few minutes' compression is enough to control it. The catheter is then removed.

Delivery Following Symphysiotomy

Immediately after symphysiotomy the fetal head is on the perineum. As saddle block anesthesia eliminates the bearing-down sensations, the patient may not be really cooperative. I therefore usually stimulate the uterine contractions by giving 1 c.c. intravenously of a solution of 1 ampule of Pitocin diluted in 10 c.c. of normal saline. There is then a good contraction of the uterus and I ask the patient to bear down with each contraction. If the second stage is going along well and the patient is cooperative, I wait for spontaneous

delivery, doing a large left episiotomy. Of course, if the patient is not cooperative or there is any indication to end the delivery more quickly, episiotomy and low forceps are performed.

The third stage and repair are performed as usual. One stitch is used to close the opening in the skin over the symphysis. A binder well tied over the iliac bones is absolutely necessary during the first week post partum.

In multiparas seen after many hours of labor with large babies and midplane dystocia, symphysiotomy is very useful and may be a real prophylaxis of uterine rupture.

Symphysiotomy never has to be performed twice on the same patient, not because the patient fearing the operation avoids pregnancy again, but because the pelvis maintains a real enlargement and all the subsequent births are normal, at least from the point of view of the pelvis.

Conclusions

1. In many cases, midplane dystocia can be anticipated in time to perform cesarean section.

2. In some cases, midplane dystocia is recognized only after many hours of labor, ruptured membranes, and complete cervical dilatation.

3. In such cases, medium forceps are usually employed and very often result in a difficult operation, with a high infant mortality and morbidity.

4. Such cases of real midplane dystocia could be managed much better if we could only get a little more room in the pelvis.

5. Symphysiotomy, if well done, can give us that necessary extra room without any damage to the mother.

6. Symphysiotomy means also a permanent enlargement of the pelvis and, from that point of view, all the subsequent births will be normal.

7. This paper is the result of 30 years of personal practice with symphysiotomy and attempts to give you an idea of how we employ this operation in Cuba.

8. Certainly, the indications for symphysiotomy are very few in obstetrics today. In my own private practice during the last year, I performed symphysiotomy 3 times in 400 births, an incidence of 0.75 per cent, or once in 133 births.

9. I have never lost a patient after symphysiotomy and, furthermore, I have never had a case of urinary incontinence or permanent difficulty in walking.

PENICILLIN THERAPY IN PRE-ECLAMPTIC TOXEMIA*

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IN JUNE, 1952, an article by Smith, Smith, and Romney[1] of Boston, appeared in the American Journal of Obstetrics and Gynecology entitled "Trials With Penicillin in the Treatment of Pre-eclampsia and Eclampsia." These authors studied the effects of large doses of penicillin in the treatment of pre-eclampsia. This mode of therapy was suggested by the discovery that penicillin showed a neutralizing effect to menstrual toxin injected into rats. The Smiths, on the basis of previous work, have long considered pre-eclamptic toxemia to be due to the release of a toxic product of tissue catabolism that apparently arises from the decidua. This toxin they feel is identical to the atypical euglobulin they have demonstrated in menstrual fluid. On the basis of results obtained in the treatment of eight patients suffering from pre-eclampsia these investigators felt that penicillin was antitoxic and did alleviate the toxemia with resultant diuresis, lowering of the blood pressure, and lessening of the proteinuria. Large doses were necessary and did not prevent death in utero nor consistently effect the desired changes. The authors readily admit that the only "cure" for the disease is the interruption of pregnancy.

A review of the recent medical literature available in English regarding therapy in pre-eclampsia is rather bewildering.[2-5] Good results may be obtained with the use of many different agents if the patient is kept at bed rest and delivered. Until the recent article already alluded to, virtually all investigators have selected some particular factor, frequently the hypertension, to treat. If penicillin does neutralize a causative circulating toxin in the pre-eclamptic patient, it would aid in preventing damage to the mother and the infant.

Method of Study

All private pre-eclamptic patients seen from early July, 1952, to early December, 1952, in any of four hospitals were placed on a penicillin† regime. A total of 12 patients were treated. Six were followed in the office prior to the development of signs of pre-eclampsia; the remaining 6 patients were first seen in consultation in the hospital after being admitted and treated by their own physicians. It was hoped that each patient could have a period of observation without therapy, an accurate record of intake and output together

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†The oral penicillin used in this study was supplied by White Laboratories, Inc., in the form of Dramcillin-500.

with a daily recording of the weight, a daily urinalysis and frequent blood pressure readings, preferably taken by the same observer. As will be seen by the brief clinical synopses that follow, it was not possible to achieve this goal. Hospitalized patients were usually started on a parenteral penicillin regime that involved initial doses of one million units of crystalline penicillin given intravenously in 500 or 1,000 c.c. of 5 per cent glucose in water and at the same time intramuscular injections of one million units every two hours. When it was considered safe or it became necessary for any reason to treat patients at home, oral penicillin in proportionately larger dosage was used. So-called conventional therapy usually consisted of a low-sodium diet, fluids freely, bed rest, and a sedative such as phenobarbital. Several of the patients seen in consultation had received hypertonic glucose by vein and magnesium sulfate parenterally.

Consultation Cases

CASE 1.—A 34-year-old woman, gravida iii, para 0, was admitted at 36 weeks' gestation in convulsions. She had had edema throughout her pregnancy, but no unusual weight gain. At 33 weeks her blood pressure was noted to be elevated; there was no proteinuria. She was given conservative therapy at home. On admission her blood pressure was 160/112, albumin four plus; she was given intravenous Sodium Amytal and intramuscular magnesium sulfate in the emergency room. Two hours later the patient was comatose; penicillin was started by vein and muscle. Vaginal examination revealed the cervix to be unripe and the patient submitted to cesarean section under local anesthesia eight hours after admission, and five hours after her last convulsion. A vigorous 4 pound, 12 ounce infant was delivered. The patient had an uneventful convalescence, and a gradual fall in proteinuria to zero on the sixth postoperative day. At the last recording, the blood pressure was 158/94. Total penicillin administered was 16,000,000 units parenterally.

CASE 2.—A 29-year-old gravida ii, para i, who had been subjected to cesarean section 15 months previously because of pre-eclampsia, was admitted at 37 weeks because of proteinuria and hypertension in spite of bed rest and sodium restriction at home. Her blood pressure was 134/98, albumin one plus, and she had no apparent edema. After 24 hours of bed rest and moderate sedation with phenobarbital, a penicillin regime was instituted. In the next 24 hours total intake was 2,880 c.c. and the output 1,600. Labor started spontaneously, but there was no progress after several hours, and the blood pressure rose to 160/100. A repeat cesarean section under local anesthesia was performed with delivery of a vigorous 6 pound, 7 ounce infant. Postoperatively the patient's blood pressure rose as high as 170/120; otherwise the convalescence was uneventful. Total penicillin administered was 11,000,000 units parenterally.

CASE 3.—A 19-year-old primigravida was admitted at 38 weeks with blood pressure 160/106, albumin four plus, and marked edema. On conventional therapy her blood pressure rose as high as 176/130. After 15 hours she was started on a penicillin regime immediately after artificial rupture of the membranes. The patient had a normal labor and delivery of a 6 pound, 2 ounce infant, and had a normal convalescence. Total penicillin was 7,000,000 units parenterally.

CASE 4.—A 24-year-old primigravida was admitted at 35 weeks with blood pressure 150/100, albumin two plus, and dependent edema. For 13 days she was kept at bed rest and given a low-sodium diet plus phenobarbital and aminophylline. The patient developed nausea, vomiting, and headache, and the proteinuria persisted. A penicillin regime was instituted and in the next 72 hours there was no change. One c.c. of Pitocin in 1,000 c.c. 5 per cent glucose in water intravenously failed to induce labor. Nausea, vomiting, and headache became worse and proteinuria persisted. Cesarean section under local anesthesia

was performed with delivery of a normal 5 pound, 6 ounce infant. Proteinuria and elevated blood pressure persisted. Total penicillin was 17,000,000 units parenterally.

CASE 5.—A 23-year-old primigravida was admitted at the thirty-eighth week, having gained 41 pounds and having failed to respond to hospitalization and the usual toxemia regime in another city. On admission her blood pressure was 150/100, albumin four plus, and she had marked edema. A penicillin regime was started and 18 hours later labor was induced by intravenous Pitocin. The patient had an uneventful labor and delivery of a normal 7 pound infant. She had a normal convalescence. Total penicillin was 18,000,000 units parenterally.

CASE 6.—A 32-year-old primigravida was admitted at term with blood pressure of 170/110, albumin four plus, and pitting edema. On conventional therapy the patient developed severe headache. Her urinary output in the first 18 hours was 785 c.c. with an intake of 2,900 c.c. At this time the penicillin regime was instituted and the membranes were artificially ruptured. After 8 hours of labor and no progress, the patient delivered by cesarean section under local anesthesia. She bled excessively and was given a 1,000 c.c. whole blood transfusion. She delivered a normal 8 pound, 4 ounce infant. During labor her intake was 1,260 c.c. and her output 440 c.c. After delivery she had an indwelling urethral catheter but was anuric for 15 hours in spite of 1,500 c.c. of glucose in water and the 1,000 c.c. of whole blood by vein. She had satisfactory diuresis and convalescence thereafter. Total penicillin was 12,000,000 c.c. parenterally.

Office Cases

CASE 7.—A 27-year-old Negro primigravida gained excessively in early pregnancy and showed a tendency to hypertension in the second trimester. At 37 weeks she developed a trace of albumin, blood pressure of 140/85, and epigastric distress. The patient was hospitalized five days and put on a penicillin regime. Attempts at induction with intravenous Pitocin failed twice, and she was discharged on oral penicillin, 3,000,000 units four times daily. She was readmitted to the hospital in the thirty-ninth week where daily urinalysis revealed two to three plus albumin and diastolic pressure remained at 90 mm. or above. Intravenous Pitocin again failed and she was submitted to cesarean section under local anesthesia. She delivered a normal 6 pound, 14 ounce infant and had a normal convalescence. Total penicillin was 116,000,000 units (8,000,000 parenterally and 108,000,000 orally).

CASE 8.—A 27-year-old gravida ii, para i, who gained excessively in spite of having lost her first baby as a result of toxic premature separation of the placenta, was admitted to the hospital at 34 weeks because of edema, blood pressure of 140/90, and a 5 pound weight gain in 48 hours. She was discharged on oral penicillin, 6,000,000 units daily, as an ambulatory patient, and was seen every three or four days until she developed a faint trace of albumin at 37 weeks. She was admitted, labor was induced, and she delivered of a 7 pound, 3 ounce infant. The patient had a normal convalescence. Total penicillin was 60,000,000 units orally.

CASE 9.—A 22-year-old gravida ii, para i, who had been delivered by cesarean section because of eclampsia at 34 weeks in her first pregnancy, was admitted at 28 weeks. During her second pregnancy her blood pressure was 110/72 at 12 weeks, but had risen to 136/94 at 24 weeks, and 180/120 at 28 weeks. At this time albumin appeared in the urine and peripheral edema was apparent. The patient was hospitalized and given sedation and large doses of dienestrol. A penicillin regime was started and intake and output carefully charted, and the result was not remarkable. Her blood pressure was 160/90 to 240/120 with persistent proteinuria. After six days the patient was discharged to allow transfer to another hospital. She was re-admitted after 48 hours and the penicillin regime was re-instituted. The patient carried to 34 weeks' gestation. Proteinuria increased and diastolic pressure was consistently above 120 mm. Under local

anesthesia cesarean section and bilateral tubal ligation were performed with delivery of a vigorous 1 pound, 9 ounce baby that survived seven days. The patient had a fairly uneventful convalescence. At ten weeks post partum her blood pressure was 130/85 and the urine negative. Total penicillin was 182,000,000 units (72,000,000 units parenterally).

CASE 10.—The patient was a 19-year-old primigravida said to be diabetic. She had no glycosuria and her fasting blood sugar was 87 mg. per cent. She gained excessively in spite of frequent visits and her blood pressure fluctuated from 110/70 to 150/95. At 38 weeks with blood pressure 150/95 and urine negative, she was put on oral penicillin, 3,000,000 units daily. On this medication as an ambulatory patient she developed severe headache and epigastric distress and was admitted to the hospital and labor was induced. The patient had a normal labor with delivery of a normal 6 pound, 6 ounce infant, followed by a normal convalescence. Total penicillin was 12,000,000 units orally.

CASE 11.—A 24-year-old primigravida had a normal course until 28 weeks, at which time she gained 8 pounds in 2 weeks and her blood pressure rose from 110/70 to 130/80. Her weight was controlled but the blood pressure steadily rose to 165/105 and albuminuria appeared. She was hospitalized and a penicillin regime was instituted at 32 weeks. Dienestrol, 40 mg. daily, had been started at 28 weeks and this was increased to 120 mg. daily. Her blood pressure gradually fell to 130/80 but albuminuria persisted. She was discharged and followed daily at home until 36 weeks, at which time she was re-admitted and subjected to cesarean section. She delivered a normal 4 pound, 15 ounce infant. The patient had a normal convalescence. Total penicillin was in excess of 200,000,000 units (24,000,000 parenterally).

CASE 12.—A 22-year-old primigravida had been known to have an interauricular septum defect that did not prevent normal activity. She did have some cyanosis of the lips and nailbeds and a harsh systolic murmur was heard at the apex and along both sternal borders. At 34 weeks she had gained 23 pounds and her blood pressure had risen from 110/70 to 130/90. On home therapy she lost 8 pounds in 8 days but at 36 weeks she showed albuminuria and her blood pressure was 160/110. She was hospitalized and conventional therapy started. After 24 hours her output was adequate but albuminuria and hypertension persisted. A penicillin regime was instituted and the membranes were ruptured artificially. She had a normal labor and was delivered of a 4 pound, 5 ounce infant. Her convalescence was complicated by cystitis. Total penicillin was 12,000,000 units parenterally.

Comment

There were no maternal deaths and 11 of 12 infants survived. To us penicillin alone did not seem to alter appreciably the course of the pre-eclampsia in any instance. Whether or not large doses of penicillin offer any protection for the baby has not been established. These mothers were delivered with little sedation and no general anesthesia when prematurity was a possibility. Seven women were subjected to cesarean section. Two had been previously sectioned, three failed of induction or progress, and in two induction was considered unwise, and these were submitted to surgery, electively. This is admittedly a high cesarean section rate. Perhaps the fetal salvage justifies it.

Most obstetricians feel that pre-eclamptic toxemia is not entirely preventable. Many will accept an occasional case of eclampsia as inevitable. Hamlin, presently the Medical Superintendent at the Women's Hospital in Sydney, Australia, has recently been able to eliminate eclampsia entirely in

5,000 consecutive clinic maternity patients, and at the same time reduce the incidence of severe pre-eclampsia to such a degree that no patient in this series required a cesarean section because of pre-eclampsia.[6]

Conclusions

1. Twelve patients with pre-eclamptic toxemia of varying degree have been given large doses of penicillin both parenterally and orally.

2. In our opinion any beneficial effect noted was equivocal.

3. The possibility of penicillin exerting an antitoxic action in pre-eclamptic toxemia certainly deserves further study.

4. Prevention of pre-eclampsia is the logical and most promising means of combating the problem at this time.

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Discussion

DR. FRED L. ADAIR, Maitland, Fla.—Only a few decades ago one of the frequent major obstetric problems was the emergency management of eclampsia. The therapy then was evacuation of the uterus, by surgical means such as induction of labor, or by more vigorous methods such as manual dilatation of the cervix by the Bossi dilator or other violent means. Less crude methods employed Dührssen's incisions, vaginal cesarean section, or podalic version and extraction. Adjuvant methods of a surgical character such as bloodletting were also used.

Many years ago it was recognized that all convulsive seizures during pregnancy were not necessarily due to eclampsia. It was also established that there were certain prodromal signs and symptoms which usually preceded the convulsive attacks, such as edema, urinary changes, the alteration of arterial tension and certain subjective symptoms, headache, visual disturbance, etc.

Changing concepts of the disease have brought nonsurgical procedures such as the therapy of the convulsive or eclamptic state and prophylactic prenatal care. The observation of women during pregnancy, with routine examination of urine, blood pressure, weight, edema, and other symptoms and signs at first led to the belief that eclampsia could be prevented. In part this was true, since by supervision the subsequent convulsive attacks can be eliminated in most instances.

The clinical picture was at first confused by the inclusion of other conditions which simulated pre-eclampsia. Such disorders were in general those which existed in women quite independently of pregnancy but which might complicate pregnancy. The picture is still complicated in spite of much study.

This disorder is peculiar to pregnancy and is, indeed, more or less peculiar to a particular pregnancy, since the same woman may have it in one pregnancy and not in others.

It is generally accepted that the only real cure for this disease is the termination of pregnancy, either by death of the fetus or by the emptying of the uterus. It also seems to be true that pregnancy may temporarily aggravate or light up hypertensive disease or renal disorders which are pre-existent.

Dr. Taylor has cited the work of Smith and associates and the theory advanced in behalf of the use of penicillin and terramycin in cases of pre-eclampsia and eclampsia; namely, the supposed detoxification of alleged decidual toxins theoretically responsible for the toxemia. It is my opinion that the Smiths' eight cases were not well chosen as test examples. Diverse forms of additional treatment were used in conjunction with the penicillin therapy. There were other circumstances which could vitiate the validity of their conclusions. In two cases there was intrauterine fetal death which was associated with the improvement, though the apparent change for the better did precede the loss of fetal heart tones. It is of course well known that fetal death often leads to improvement in these toxic cases.

In comment the Smiths write: "Interruption of pregnancy remains the only cure for toxemia, but in the critically ill patient penicillin might make this a safer procedure than it would be otherwise." With the first part of this statement I can agree but the main question is what to do in the meantime and when and how to end the pregnancy. As to the second conclusion I remain skeptical.

Prevention of the toxemias is the ideal, but so far as I know we have been able only to avert the more serious stages of pre-eclampsia and eclampsia by rest, sedation, proper hygiene and nutrition, avoidance of infections and other harmful disorders during pregnancy, and by symptomatic therapy. By these measures and the selection of appropriate means at the proper time for the termination of pregnancy, it has been possible to alleviate the symptoms and avoid the eclamptic seizures in nearly all instances. Thus the fetal and maternal as well as the neonatal morbidity and mortality have been reduced to the present lower level. The final means of prevention or cure of the toxemias must await the discovery of the cause and the means of its elimination or neutralization.

DR. ERNEST W. FRANKLIN, Charlotte, N. C.—It has been believed for some time that there is some toxic substance peculiar to pregnancy that alters the body physiology to a certain degree, producing a toxemia of late pregnancy. It has been known that this toxin also at times alters certain pathological conditions of the circulatory system, the renal system, and the hepatic system. The search for this substance has been tireless.

The short series that Dr. Smith has presented does not necessarily prove that he is on the right track nor does the short series presented by Dr. Taylor totally disprove Dr. Smith's work. Studies with larger series may give us a clearer understanding of this mechanism and the use of penicillin may be more efficacious than it seems at this time. In recent years we have had so many new and wonderful therapeutic agents for the treatment of diseases in all fields of medicine that I am hopeful that some will prove most helpful in this scourge of the obstetrical patient.

There has been some interest in the use of cortisone. A study reported in the *British Medical Journal* by Moore of Dublin on the use of cortisone in twelve cases of toxemia of late pregnancy gave a result about as equivocal as that of Dr. Smith's series of cases of eclampsia treated with penicillin. In Moore's series, the use of cortisone was somewhat paradoxical, for although its use produced some retention of electrolytes, sodium, and potassium, there was some improvement in the patient for short periods of time. Our knowledge of water and electrolyte balance has increased tremendously in the last few years. This is of course useful, but it seems to result in the treatment of symptoms rather than of cause. The same might be said for those preparations that lower blood pressure. They are a temporary stopgap until the delivery of the baby can be accomplished; they help us to borrow time for the maturity of the infant. The use of continuous spinal anesthesia or continuous caudal anesthesia falls somewhat in the same category but none of these preparations seem to reduce the albuminuria and prevent the loss of proteins as Dr. Smith reports in his use of penicillin.

DR. FRANK R. LOCK, Winston-Salem, N. C.—Drs. Taylor and McCall have made a real contribution in undertaking a study to confirm the effect of massive penicillin therapy

in toxemia of pregnancy. Their observation does not confirm the published report of Dr. George Van S. Smith and it appears that the use of penicillin in the treatment of toxemia of pregnancy was worthless. We have used Dr. Smith's regime on the obstetric service of the Bowman Gray School of Medicine of Wake Forest College and the North Carolina Baptist Hospital on several occasions, and have never observed any improvement in the condition of the patient.

The author of any article which recommends a new plan of treatment in a serious medical condition must appreciate the responsibility he must bear in the matter of the public welfare. Physicians in general rely upon those of us who hold teaching and research appointments to establish fully the value of a new therapeutic procedure before it is offered to them through the current literature. We must also appreciate that our therapeutic recommendations will be further disseminated by the representatives of pharmaceutical houses, and articles appearing in obscure or highly technical journals reach the general practitioner when their content suggests something of commercial value.

The files of the Committee on Maternal Welfare of the Medical Society of the State of North Carolina contain at least 6 records of women who died of toxemia of pregnancy whose primary treatment was with the penicillin regime published by Dr. Smith. Although it is debatable that their lives might have been saved by standard treatment, it is the opinion of our Committee that they would have had a better chance of survival with the advantage of standard treatment.

I am afraid that the observations of Drs. Taylor and McCall will not receive the widespread attention that they deserve, but certainly their study will have some effect upon the impression that penicillin is of value in the treatment of pre-eclamptic toxemia of pregnancy.

Until there is further evidence, the use of this drug for treatment of toxemia of pregnancy should be restricted to further study in research institutions under carefully controlled conditions.

DR. TAYLOR (Closing).—I am grateful to the discussants for their comments. Dr. George Smith was kind enough to send me a copy of his latest paper which will be published this spring. In it he and his co-workers have shown that in their hands terramycin is quite as effective as penicillin in its antitoxic effect. They also noted that terramycin causes an increased excretion of sodium and potassium.

CLASSIFICATION OF HUMAN PREGNANCY BASED ON DEPTH OF INTRAUTERINE IMPLANTATION OF THE OVUM*

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(From the Department of Obstetrics and Gynecology, Medical College of Georgia)

THIS paper is a report of investigation upon the subject of human placentation which began with the discovery of an unusually perfect specimen of placenta circumvallata in the year 1930. Not having any preconceived ideas of its development, and, in fact, very little knowledge of it whatsoever, I immediately formulated a rational concept of how it formed, knowing that such an extensive anomaly must have originated very early in the embryonic development. The hypothesis that presented itself was that in the early stage the placenta had been so extensive that it covered more than one-half of the fetal sac, that the fetus had been unable to dilate the placental cavity thus formed and had instead distended the membranes over the free area and had herniated from the placental cavity through the resulting placental ring into the dilatable membranes. All of this occurred within the uterine cavity with pulling off of the excess placenta so that a ring of dying or dead chorionic tissue with its overlying decidua was pushed back to lie over the marginal face of the active placenta.

A paper[1] was presented upon the subject before the Chicago Gynecological Society in 1931. This paper brought out the relationship to marginata and to normal placental formation but not nearly so many facts in regard to implantation were then known as now. In the intervening 21 years constant study has been devoted to ascertaining facts pertinent to the development of these placental anomalies and their interrelationship. Certainly many of the conditions seen in the term placenta have their origin at the time of implantation. For instance, it has long been known that attachment of the ovum low in the uterine cavity gives rise to placenta previa. Furthermore, by a sac-distention method[2] in which models made to scale of the placental site, size, and intrauterine relationship were demonstrated in 1,150 cases, 8 per cent were found to be bilobate[3] to a greater or less degree and almost all of these were in those cases in which the ovum implanted in or near the crease between the anterior and posterior relatively flat uterine walls. This corresponds to Heuser's[4] 44 macaque cases, all implanted on the anterior or posterior wall with the exception of 3 on the lateral groove.

In the 1931 paper I assumed that these sulcus implantations might be marginate in type and that the circumvallate placentas were those which implanted immediately inside of the uterine horn area ("Tubenecke," Bayer, 1911).[5] Since then I have found most of the circumvallates to be implanted

*Presented at the Fifteenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Havana, Cuba, Jan. 29,30, 31, 1953.

upon the anterior or posterior flat uterine wall. Dees Mattingly[6] carefully described and illustrated one such case in a 5 months pregnant uterus (1939). In a series of nearly 100 pregnant uteri hardened in formalin prior to opening I have found one or two excellent specimens on the flat wall.

Whitridge Williams[5] saw no relation between placenta circumvallata and placenta marginata, in the latter of which anomalies there is a circumferential ring of necrotic villi with a layer of decidua underneath. However, if one takes the trouble to study several thousand fresh placentas he will be struck by the fact that one type shades into the other and that occasionally it will be difficult to decide what to name some of these borderline cases. If a circumvallata has a small area within the ring, then the ring is much more likely to be thick and well developed. The greater this area is, the less likely will the margin be prominent and then it approaches the appearance of a well-developed peripheral ring of whitish necrotic material of the marginata placenta.

In an investigation of 5,000 odd fresh placentas it was found that normal-edged placentas occurred in approximately 75 per cent of all of those implanted upon the relatively flat anterior or posterior uterine wall, and that approximately 23 per cent were marginate, total, or in part of the circumference, and that 1 to 1.5 per cent were definitely circumvallate. Most likely a certain percentage of circumvallatas arise in the uterine horn areas as previously mentioned. Slowly, over the years, as this study progressed, it has occurred to me that there must be a variation in the depth of implantation of the ovum into the endometrium in some cases, especially where there is some degree of hyperplasia or possibly hypoplasia. Lahm,[5] in 1924, advanced a similar idea as to the cause of the formation of placenta circumvallata.

It probably may be stated as an axiom that the chorionic villi will grow, thrive, and ultimately form placental tissue if they are contiguous with decidua of adequate maternal blood supply. Therefore, the deeper implantations with more villi lying adjacent to maternal blood sinuses should have subsequent placentation covering a greater area of the early ovular sac than more superficially implanted ones.

What evidence is there for a variation in depth of ovular implantation? If one asks the chief students of this phase of embryology he will find them at a loss for a definite answer. The reason for this is possibly that they have not given this particular subject much study, but chiefly because almost all primate implantations are very superficial.

In the human being and anthropoid apes, implantation is ordinarily interstitial,[7, 8] embedding completely into the decidua very superficially but enough to form a decidua capsularis. In most of the monkeys, catarrhine and platyrrhine, implantation is more superficial so that no capsularis is formed and, in most cases, but not all, the exposed surface of the blastocyst allows the chorionic villi to grow into the adjacent opposite uterine wall decidua, thus resulting in the well-known primary and secondary placentas so well illustrated in the macaque. There may be, however, transition of one type to the other occurring in individuals of almost every species. Wislocki,[7]

in 1929, stated: "In man and the anthropoids a capsularis is concerned in establishing the ultimate placental form. In monkeys in which the ovum does not become implanted in the mucosa, but in the uterine cavity in contact only with one or both uterine walls without the formation of a capsularis, the form and position of the placental disks is the result of a different mode of implantation than that occurring in anthropoids. From our knowledge of the early stages of the development of the monkeys (Selenka, Kollmann, Duckworth, Strahl, Wislocki), circumscribed discoidal contacts at one or both poles occur early and remain relatively unaltered. Hence the discoidal form in monkeys may be looked upon as primary; whereas in the anthropoids the placenta in association with the formation of a capsularis is primarily globoid and diffuse, and becomes reduced secondarily to the single discoidal or intermediate forms. Hence the derivation of discoidal forms in monkeys should not be confused with their formation in anthropoids, for in these latter the discoidal forms constitute a special case. Nevertheless, from the observations

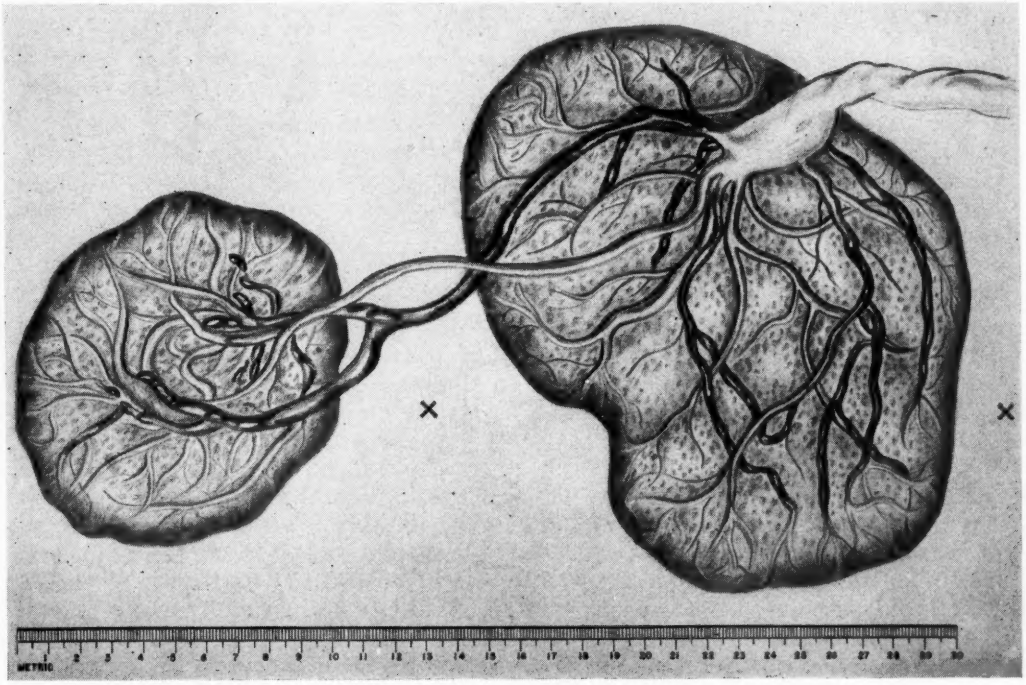

Fig. 1.—Primary and secondary placentas, one on anterior and one on posterior wall, in the human being, similar to that ordinarily found in the macaque. The X's mark the lateral border of the uterus.

of Selenka and Strahl upon the presence of a possible capsularis incompleta in some monkeys, we are led to believe that transition forms between the two types of implantation exist, the ovum in some instances burrowing its way into the mucosa only very superficially with the production of an incomplete capsularis. Theoretically, some of the double forms in the human might find their true explanation in superficial and faulty implantation resulting in the formation of an incomplete capsularis or none at all; in this case the condition

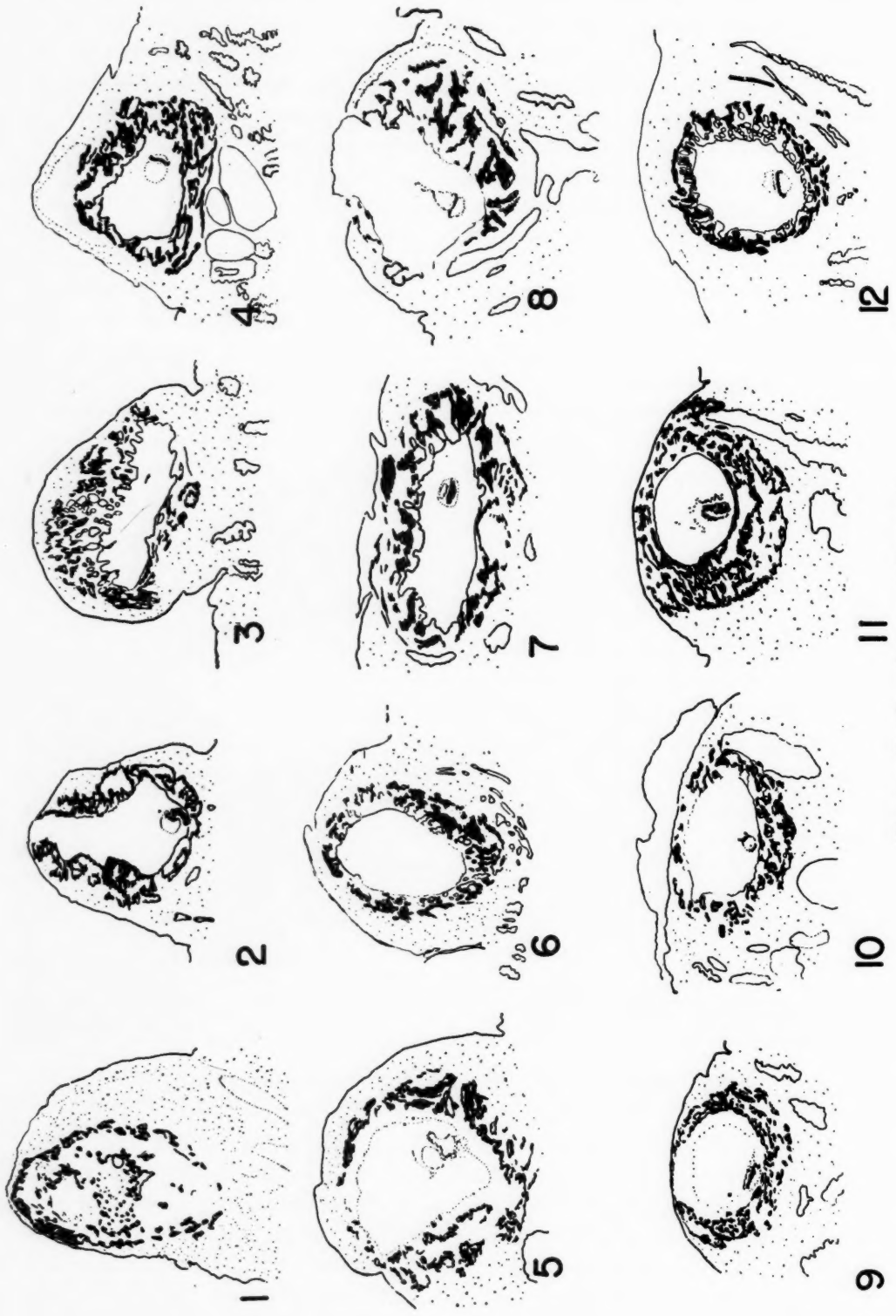

Fig. 2.—*(For legend see opposite page.)*

would be homologous with that which is normal for monkeys. It is doubtful, however, whether the anthropoid ovum would survive surface or extremely superficial implantation."

Contrary to Wislocki's last sentence there is proof that very rarely in the human being a similar thing happens to that in the macaque, and the woman then has primary and secondary placentas, one on one wall and one on the opposite wall of the uterus (Fig. 1). Hyrtl illustrates one such in Davis' *Gynecology and Obstetrics.*[9] Furthermore, a perusal of the known early human implantations shows some to be much more superficial than others (Fig. 2). If there is a variation in depth of implantation, it could very well be described roughly in four types, each of which effects distinct results as determined by the termination of the pregnancy, in certain instances in abortion or in placental characteristics at term. These four types are as follows:

Type I.—Very superficial implantation as in Fig. 2, Nos. 1, 2, and 3. In many cases these probably never acquire enough maternal blood nutrition to exist long and, therefore, abort in a few days giving rise to what is thought to be a delayed period. Rarely, however, one may supplement the scanty primary placenta with a secondary one on the opposite wall as in Fig. 1.

Type II.—This type represents the great bulk of normal pregnancies in which implantation is deep enough to obtain living, active chorionic villi to form a placenta, constituting approximately one-fourth of the area of the ovular sac of all anteriorly and posteriorly implanted human pregnancies and the placenta, at term, is discoid, of fairly uniform size, and has no evidence of disruption at the margin; the amnion, chorion, and decidua all shade off the placenta into the membranes without infarction at the margin. This occurs in roughly 75 per cent of all human pregnancies which go to term.

Type III.—In this type it is postulated that the ovum implants deeper than in Type II, and up to one-half of the villi are able to acquire maternal blood supply and then the subsequent early placenta covers more than 25 per cent and less than 50 per cent of the sac. Therefore, these must be reduced in size by a gradual slipping off of the growing, excessive, placental margin which is constantly being laid down at the edge in an ever-increasing white band of necrotic villi. This also explains the previously inexplicable layers of decidua external to the marginate ring. Proof of this development may be had by observation of a series of sacs in cases of acute hydramnios at or near term. The sudden increase in size of the uterine cavity is associated with abrupt stretching of the uterine wall and the margin of the placenta, unable to expand so rapidly, is slipped off and forms a wide band of total circumferential margination. (I have many models of such a condition.)

Fig. 2.—
1. Carnegie Inst. Ovum 7771, 3-4-1, 13 day abnormal, Hertig and Rock.[13] (×100.)
2. Carnegie Inst. Ovum 8299, 11-6-5, 13 day normal, Hertig and Rock.[13] (×100.)
3. Studdiford Ovum X? 17 day? Abnormal.[14]
4. Carnegie Inst. Ovum 7801, 12-1-1, 13½ day normal.[15] (×35.)
5. Torpin Ovum (Krafka). 13 day normal.[16] (×150.)
6. Latta-Tollman Ovum, no embryo found. Est. 17 day.[17] (×18.)
7. Yale embryo. Normal, 13 day.[18] (×30.)
8. Biggart Ovum. Normal, est. 17½ day.[19] (×38.)
9. Carnegie Inst. Ovum 7700, 5-7-7. 12½ day normal.[13] (×100.)
10. Edwards-Jones-Brewer Ovum. 15 day normal.[20] (×275.)
11. Carnegie Inst. Ovum 8299, 11-6-5. 12 day normal except position of embryo.[13] (×100.)
12. Carnegie Inst. Ovum 7002, 44-3-5. 16½ day normal.[15] (×30.)

Type IV.—This type is that one, more rare than the others, in which the implantation is deep enough to permit adequate maternal blood nutrition to more than half of the primitive villi, so that the subsequent early placenta covers more than half of the ovular sac. This condition is not infrequently

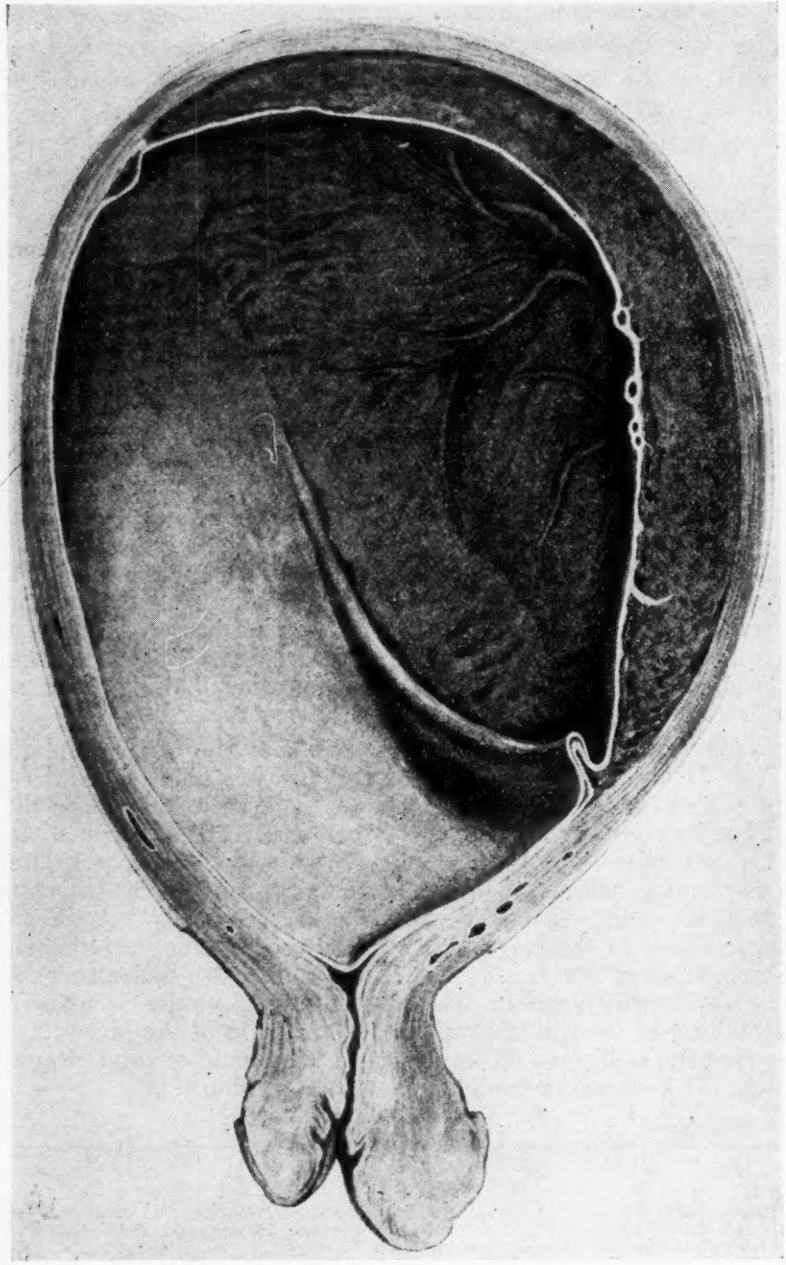

Fig. 3.—Production of a placental marginal fold reproduced from Liepmann, 1906.[10]

seen in 3 to 4 month abortion sacs. Inasmuch as the placental cavity thus formed cannot dilate, the amniotic contents, if the pregnancy is to continue, distend the thin membranes covering the area free of placenta and the fetus

and amniotic fluid literally herniate from the placental cavity through the ring formed at the margin and, since all this takes place within the uterine cavity, the excess placenta is pulled off the uterine wall and pushed back onto the face of the active placenta. The circumvallate ring then has all of the structures one would expect from this hypothesis and, likewise, the two layers of decidua are here explained as in the case of marginata, Type II.

In extremely rare instances the whole blastocyst may be covered with active proliferating villi with adequate maternal decidual blood supply so that the early placenta completely surrounds the whole sphere of the fetal sac originating in placenta membranacea. In 17,000 labors and their attendant number of abortions I have not encountered a recognized instance of placenta membranacea. However, Cross[21] informs me that he has seen three cases in the past few years, all of which aborted in the latter part of the first trimester or in the second trimester.

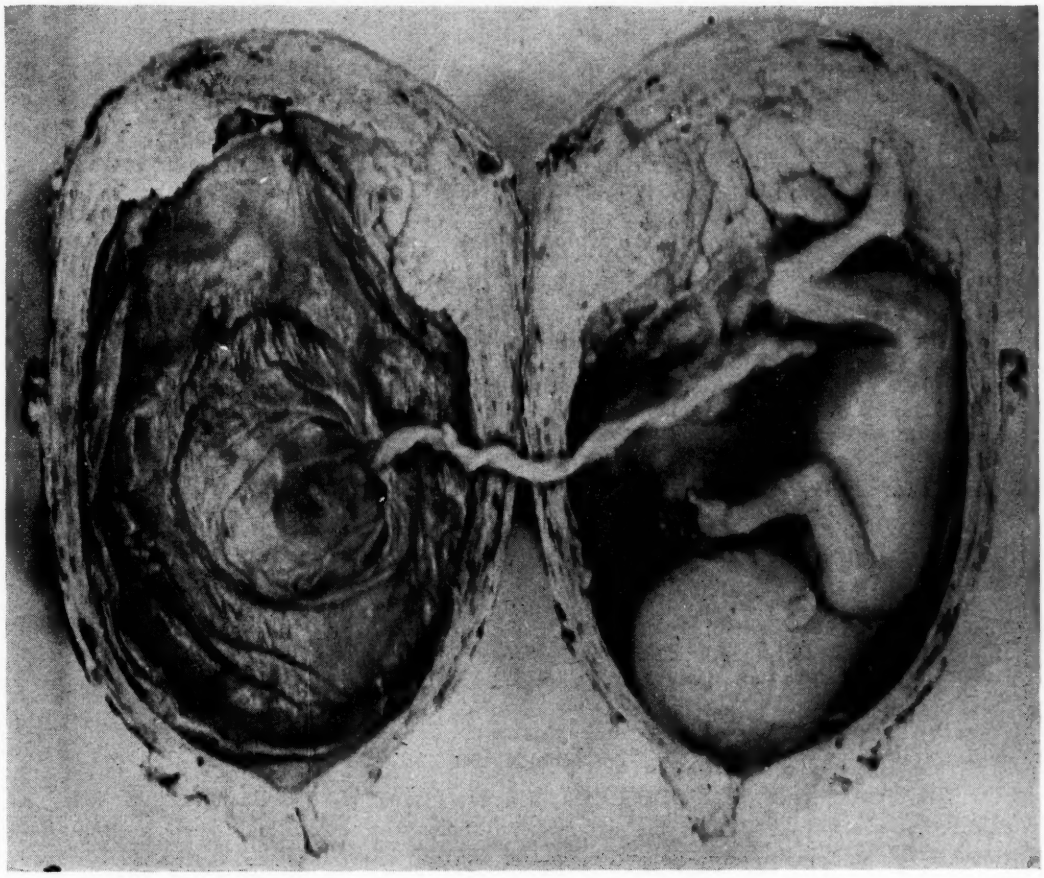

Fig. 4.—Placenta circumvallata in process of formation. Four months pregnant uterus. Note extensive degree of decidual hyperplasia at the apex of the fundus.

Liepmann,[10] in 1906, reported four pregnant uteri with rings in the process of formation (Fig. 3). I have found several similar cases. Hobbs and Rollins[11] and Hobbs and Price[12] have stated from their clinical studies that approximately one of three pregnancies with circumvallate placentas abort or have premature labor, and my experience indicates a much greater

fetal loss. One readily notes that in pulling the placental margin loose from the uterine wall, the decidual maternal vessels are ruptured and more or less retroplacental marginal hemorrhage takes place. This is of greater import in the extensive separation in placenta circumvallata, but also has been found to lead to abortion or to premature separation of the placenta in the marginate type. A careful observation of the ovular sac in several hundred cases convinces me that this is the anatomic etiology of most abortions which occur late in the first trimester.

Now a few words in regard to the primary etiology for possible variations in depth of implantation. In two cases of circumvallata there was associated an extreme degree of fungating hyperplasia of the decidua (Fig. 4). In one, at term, the decidua was so excessive that it was thrown up into many polyps, one of which was as thick as and longer than a man's thumb. It is possible that varying degrees of endometrial hyperplasia may account for the conditions described. It would be interesting to ascertain the comparative abortion rate of women with and without endometrial hyperplasia. There should be a re-evaluation of the finer points of endometrial variations.

I wish to acknowledge the invaluable counsel of Chester H. Heuser and the aid received from many discussions throughout the years with Lester Bowles and Joseph Krafka, Jr.

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Discussion

DR. JOSE RAMIREZ OLIVELLA, Havana, Cuba (By invitation).—There is no doubt that the extremely variable size and morphology of the placenta have a close relationship to the fetal sac and depend ultimately on the distribution of chorionic villi over the sac. This line of reasoning explains the diffuse placenta of the ungulates (pig, horse), the cotyledonal placenta of the ruminants (cow, sheep, deer), the zonal placenta of the carnivora (cat, dog, lion, fox, bear) and the discoid placenta of rodents and anthropoids in which chorionic villi scattered in early pregnancy become finally limited to an area with a discoid shape.

If we study the placentas according to their structure, their physicochemical and histological relationship with the uterine wall, they can be grouped in five types as follows:

1. Epithelial-chorionic of the ungulates
2. Syndesmochorionic of ruminants
3. Endothelial-chorionic of the Carnivora
4. Hemochorionic of the inferior rodents and primates characterized by an extensive erosion and destruction of the uterine mucosa.
5. Hemoendothelial of the superior rodents.

Considering Type 4 we should note that the chorionic villi erode the uterine mucosa forming pools in which they bathe in maternal blood from the open vessels. Chorionic and uterine tissues are so interlaced that during labor the placenta becomes detached as a unit and a layer of degenerating mucosa remains beneath. The human placenta is a variant of this type and due to the fact that the ovum becomes embedded in the uterine mucosa or decidua it is known as an interstitial implantation.

Due to our great interest in the shape of the human placenta we suggested to Dr. Galvez from our former service in "Maternidad America Arias" that we study 10,000 human placentas. We considered the different depths of implantation of the ovum in the uterine mucosa, the muscularis, and the more invasive forms in which the ovum burrows its way to the peritoneum, but we did not study the variations in depth of implantation of the ovum in the different layers of the mucosa as was done by Dr. Torpin.

Dr. Torpin has established four different types according to the depth of implantation of the ovum in the uterine mucosa. He includes in the first those with very superficial implantation which on account of not acquiring enough maternal nutrition yield a great number of abortions mistaken as delayed periods. The second group comprises those embedded somewhat deeper in the mucosa (an interstitial implantation) which are consistent with normal pregnancy, and finally Types III and IV in which the depth of implantation of the ovum is greater and which produce the marginate and circumvallate types of placenta.

The variation in depth of implantation of the ovum must itself be conditioned by individual variation in the eroding power of the trophoblast or by the different phases of the menstrual cycle at the precise time of nidation of the ovum, disregarding of course those implantations on pathologic mucosa.

In reference to the question raised in Dr. Torpin's paper about evidence for a variation in the depth of ovular implantation, I think it fitting to go back to the study I carried out from 1940 to 1943. In that study of 10,000 placentas we correlated the different depths of implantation of the ovum in the mucosa or muscularis with the eroding power of the ovum, grading such power in three groups:

1. Hypoactive ova with diminished eroding power. This group includes those cases with scanty production of tryptic enzyme, corresponding to Torpin's Type I.
2. Normoactive ova, with normal eroding power similar to Torpin's Type II.
3. Hyperactive ova which produce Dr. Torpin's Types III and IV, and which, according to our hypothesis due to their great eroding power, give rise to placenta accreta with its three variants: accreta proper (implanted superficially in the muscle), increta (implanted interstitially in the muscle), and hypercreta (deeply implanted in the muscle and with power enough to perforate it). Needless to say our hypothesis implies a breakdown of the balance between the tryptic activity of the trophoblast and the antitryptic enzymes of maternal orgin.

The occurrence of placenta marginata, circumvallata, or simply vallata, has been considered by Schatz to depend on a superficial implantation with a narrow base, while Lahm on the contrary claims a rather deep implantation. We do not support Schatz's viewpoint and are inclined with Torpin to postulate a deeper implantation in which more than half of the primitive villi receive adequate maternal blood nutrition, originating the sequences which he depicted in Type IV.

Sfameni and Olesen, quoted by Hinselmann, state that placenta circumvallate is not a predisposing cause of abortion and that it does not interfere with normal development of the

fetus. In the cases we have seen we did not notice any defect in the newborn. In our experience the same holds true for placenta accreta which we included in Group 3 of our classification of the ovum according to its eroding power.

Finally, we are tempted to state that the eroding power of the ovum in the early stages of its implantation should be related to the cellular layer of Langhans rather than to the syncytial layer, because the former disappears in the process of nidation of the ovum while the latter persists.

The paper presented by Dr. Torpin is very interesting indeed and the concepts presented by him about the depth of intramucosal implantation of the ovum are to my knowledge absolutely original.

THE TREATMENT OF INFERTILITY IN PRIVATE PRACTICE WITH EMPHASIS ON HYSTEROSALPINGOGRAPHY*

JOHN H. E. WOLTZ, M.D., W. Z. BRADFORD, M.D., WALLACE B. BRADFORD, M.D., AND CHARLES W. BROWN, M.D., CHARLOTTE, N. C.

THE treatment of infertility will vary widely among private practitioners of obstetrics and gynecology. Of all the branches of our specialty, there is probably none in which so many diagnostic and therapeutic measures are available; and probably none where inclination and prejudice play so important a role in their selection.

One of the procedures we use most frequently is hysterosalpingography. For the purpose of discussing the subject of infertility treatment, we have selected 100 consecutive patients in whom hysterosalpingograms were done. The hysterosalpingogram is the only consistent factor in the analysis of these 100 cases.

The division of responsibility between husband and wife in sterile matings is about equal. The responsibility of the male in these 100 couples was determined by semen analysis in 49 cases. According to Farris,[1] a count of at least 83,000,000 spermatozoa per entire specimen with normal motility and morphology is considered adequate for fertility. It is important that a semen analysis be carried out as a precise laboratory technique. A casual glance at a drop of semen under the microscope is inadequate in determining the fertility of any male.

Table I shows that 4 of these males came in the group considered highly fertile, that is, with a count of over 185,000,000 per total specimen. Thirteen of this group came into the relatively fertile group, which is from 83,000,000 to 185,000,000, and 32 of this group had counts averaging 31,000,000, which is considered subfertile. Two had complete aspermia. Thus, two-thirds of the male partners examined in our series were subfertile. Unfortunately, there is no satisfactory treatment for these relatively infertile males. There is no treatment that will make a good specimen out of a poor specimen. Heckel and McDonald[2] have treated oligospermia with large doses of testosterone. A rebound phenomenon of spermatogenic activity after azoospermia produced by testosterone is the suggested basis of their treatment. We have not advised this form of therapy.

Table II shows the percentage of pregnancies resulting in the fertile as compared to the subfertile group. In the fertile group of 17, 13 pregnancies, or 76 per cent, resulted. In the subfertile group of 34, 18 pregnancies, or 53 per cent, resulted.

*Presented at the Fifteenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Havana, Cuba, Jan. 29, 30, 31, 1953.

TABLE I. CLASSIFICATION OF CASES ACCORDING TO SPERM ANALYSIS

NUMBER OF MOVING SPERM IN TOTAL EJACULATE	NUMBER OF CASES	ACTIVE SPERM	ESTIMATED DEGREE OF FERTILITY
More than 185,000,000 (Group I)	4	255,000,000	Highly fertile
83,000,000-185,000,000 (Group II)	13	117,000,000	Relatively fertile
Under 83,000,000 (Group III)	32*	31,000,000	Subfertile

Aspermia, 2.

TABLE II. PREGNANCIES RESULTING IN MALES WITH DIFFERENT SPERM COUNTS

	NUMBER OF CASES	RESULTING PREGNANCIES	
		NO.	%
Fertile (groups I and II, over 83,000,000)	17	13	76
Subfertile (group III, under 83,000,000)	34	18	53

Artificial insemination is a controversial subject from the standpoint of indications, methods, and interpretation of results. The object of insemination is thought to be the increasing of the number of spermatozoa which penetrate the cervical os. Fourteen patients were inseminated in the uterus with 0.25 to 0.5 c.c. of their husbands' fresh, undiluted semen, using an antrum cannula and tuberculin syringe. Our criteria for insemination have been (1) failure of conception after a reasonable length of time following sterility investigation of both partners, and (2) a male partner who is considered subfertile. Table III shows that 6 pregnancies resulted, which gave us a 47 per cent success in this discouraging group.

TABLE III. RESULTS FOLLOWING ARTIFICIAL INSEMINATION

PATIENT NO.	SPERM IN MILLIONS	PREGNANT	PATIENT NO.	SPERM IN MILLIONS	PREGNANT
18	9.5	No	59	21	No
12	8	Yes	80	11	No
24	39	Yes	84	6	No
25	53	Yes	93	20	No
40	36	No	95	76	Yes
45	43	No*	97	14	Yes
58	95	No*	100	8	Yes

Total patients, 14. Total pregnancies, 6 or 47%.

*Subsequently became pregnant.

The problem of anovulation is present in two groups of women. The first group is composed of women who bleed cyclically without egg production. If a premenstrual biopsy yields nonsecretory endometrium, or if a basal temperature chart shows no thermal shift, the presumption is that ovulation has not occurred in that cycle. Anovulatory women of the second group are characterized by long periods of amenorrhea. The treatment of anovulation is unsatisfactory. The object of endocrine therapy in these cases is to stimulate egg production. The only hormones that do this are gonadotropins, and unfortunately we have no gonadotropins which do an adequate job. We

therefore fall back on the steroid hormones, the estrogens and progesterone, which we must remember are the result and not the cause of the maturation and rupture of the follicle. Yet, paradoxically, enough, the employment of these hormones offers some help. Apparently such treatment has a beneficial effect on the delicate ovarian pituitary equilibrium, leading to an increased production of natural gonadotropins capable of stimulating the ovary to ovum production. Androgens and pituitary-like hormones have been used with varying degrees of success. We have not used cortisone or x-ray in these patients.

The employment of thyroid, where indicated, seems to offer encouraging possibilities. Of our 100 patients, 53 had basal metabolism tests. In sterility studies it is believed by some[3] that a basal metabolism rate over zero gives the best results. While we do not feel the role played by thyroid therapy is as important as formerly, we still use it when indicated. Table IV shows that 81 per cent of those studied had metabolism rates below zero.

TABLE IV. BASAL METABOLISM IN 53 CASES

BASAL METABOLISM RATES	NUMBER OF CASES
0 or over	10
-10 to 0	21
-20 to -10	14
-20 or less	8
Total	53
Depressed	81%

In our series there were 6 women who had anovulatory cycles and were treated with hormone therapy. Two have become pregnant. These results are shown in Table V.

TABLE V. RESULTS OF TREATMENT IN 6 PATIENTS WITH ANOVULATORY CYCLES

NAME	TYPE	TREATMENT	PREGNANT
24	Endocrine dysfunction	None	No
43	Endocrine dysfunction	Hormone	No
45	Endocrine dysfunction	Hormone	Yes
52	Endocrine dysfunction	Hormone	No
78	Endocrine dysfunction	Hormone	Yes
89	Endocrine dysfunction	Hormone	No

The ovaries of women in the childbearing age normally contain follicles in varied stages of regression. Some of these may persist as tiny retention cysts, and ordinarily such structures are of no importance. In rare cases atretic follicles accumulate to the point where it is thought an increased intra-ovarian tension makes ovulation impossible. Ovarian resection of these polycystic ovaries has been shown by Stein and Leventhal[4] often to succeed in restoring normal function.

Table VI shows the results in 5 patients with amenorrhea. Two patients with the Stein-Leventhal syndrome, who were operated upon, subsequently established normal cycles, and became pregnant. The other 3 patients showed

rather marked hormonal deficiencies, reflected most prominently in thyroid deficiency. The basal metabolism tests of 2 were minus 40 per cent and minus 22 per cent. With hormone therapy, including thyroid and substitutional therapy, menstruation was re-established, and 2 of the 3 patients have subsequently become pregnant. A larger series would doubtless not show such good results.

TABLE VI. RESULTS OF TREATMENT IN 5 PATIENTS WITH AMENORRHEA

NAME	TYPE	TREATMENT	PREGNANT
10	Stein-Leventhal syndrome	Surgery	Yes
28	Stein-Leventhal syndrome	Surgery	Yes
53	Endocrine dysfunction	Hormone	Yes
86	Endocrine dysfunction	Hormone	No
90	Endocrine dysfunction	Hormone	Yes

Hysterosalpingography has been our choice of methods of evaluating the degree of tubal patency. We feel the diagnostic value of this procedure to be superior to that of the Rubin test, and its therapeutic value in our hands seems to be important. All of these patients had hysterosalpingograms and, as Table VII shows, 65 of the 100 had essentially normal hysterograms showing bilateral patency. Of this group with normal hysterograms, 45 became pregnant, giving a percentage of 69 per cent. Of those with hysterosalpingograms where unilateral patency was demonstrated, 9 out of 19 became pregnant, a salvage of 47 per cent. Eight of these patients had bilateral closure, which is an absolute factor in sterility rarely overcome. We had no pregnancies from this unfortunate group.

TABLE VII. RESULTS IN RELATION TO TUBAL PATENCY AS DETERMINED BY HYSTEROSALPINGOGRAPHY

RESULTS	NO.	PREGNANT	%
Bilateral patency	65	45	69
Unilateral patency	19	9	47
Bilateral closure	8	0	0
Other pathology	8	2	25
Total	100	56	56

Assessment of the results of hysterosalpingography is difficult. Other procedures involving instrumentation of the cervical canal, such as dilatation of the cervix and the Rubin test, have been known for years to be frequently followed by pregnancy. The method of cure by insufflation or hysterosalpingogram has been discussed at length, and the following effects seem to be well established: first, the establishment of patency of the genital tract,

TABLE VIII. PATHOLOGIC LESIONS DEMONSTRATED BY HYSTEROSALPINGOGRAPHY

LESION	NO.
Infantile uterus	3
Bicornate uterus	2
Fibroids (submucous)	2
Hydrosalpinx	2
Total	9

then dilatation of the cervix and removal of cervical mucus, plus dilatation of the tubes, and a possible psychic effect. We have not advised surgery on closed Fallopian tubes.

Other pathology shown by hysterosalpingogram appeared in 9 patients, 2 of whom subsequently became pregnant, which gives us a 25 per cent salvage in this group (Table VIII). The over-all salvage in the 100 patients reported is 56.

Pelvic pathology, not revealed by hysterosalpingography but determined by clinical means, is noted in Table IX. A total of 38 lesions was found in the 100 patients, and these were treated by surgical or biochemical methods where indicated.

TABLE IX. PATHOLOGIC LESIONS NOTED ON PHYSICAL EXAMINATION

LESION	NO.
Bartholin abscess	1
Vaginitis	4
Cervicitis	7
Cervical stenosis	1
Myoma, subserous	2
Ovarian cyst	1
Polycystic ovaries	2
Endometriosis	5
Adherent retroversion	3
Functional uterine bleeding	4
Chronic cystic mastitis	1
Previous pelvic surgery	7
Total	38

Table X shows the interval of time between hysterosalpingography and conception. It is interesting that conception occurred 6 times the same month the test was performed and 16 times after the following menstrual period.

TABLE X. INTERVAL BETWEEN HYSTEROSALPINGOGRAPHY AND CONCEPTION

MONTHS	NO. OF PATIENTS
0	6
1	16
2 to 6	17
6 to 12	7
Total	46
Insufficient data	4
Artificial insemination	6
Total pregnancies	56

TABLE XI. RELATION OF DURATION OF STERILITY TO TOTAL SUBSEQUENT PREGNANCIES

YEARS	NO. PATIENTS	PREGNANCIES	%
½	6	5	83
1	11	8	73
2	12	6	50
3	17	10	59
4	17	13	76
5	12	7	58
6-10	15	5	33
11-15	8	2	25

Table XI gives a correlation between the duration of sterility and subsequent pregnancies. We realize that a strict definition of sterility may invalidate infertile states of under two years' duration. We feel, however, that any couple who have been unsuccessful in their attempts to conceive for six months or more are worthy of investigation. This is particularly true in the older age groups (Table XII).

TABLE XII. RELATION OF AGE TO SUBSEQUENT PREGNANCIES

AGE		PREGNANCIES	
YEARS	NUMBER OF PATIENTS	NUMBER	%
20-25	26	15	58
26-30	43	24	56
31-35	20	12	60
36-40	10	5	50
40	1	0	0

Before concluding, we should mention the psychological factors in infertility. We have seen patients who conceived after bimanual examination and no other treatment. The occurrence of a sterile woman becoming pregnant after adopting a baby is common enough to have been frequently noted. Fertility has often followed a change in working conditions and environments. All of these factors must be taken into consideration in evaluating any group of results.

Conclusions

We have presented the results obtained in 100 consecutive infertile patients who had hysterosalpingography. From this group 56 pregnancies resulted. The group is a selected one in that all were private, white patients, and further, that those infertile patients who did not have hysterosalpingograms are not included. Our methods and ideas on some of the problems of sterility are mentioned.

In view of our experiences in the treatment of infertility it seems advisable to combine the methods of treatment that appear relatively useful when employed separately. The combination of hysterosalpingography and hormone therapy, together with the correction of any gynecological pathology present and the use of artificial insemination in selected cases, offers a realistic approach to the treatment of the infertile patient in private practice.

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Discussion

DR. EARNESTO R. de ARAGON, Havana, Cuba.—Dr. Woltz and his co-workers begin by dividing the responsibility between husband and wife. Even though we find a greater frequency of responsibility in the woman, this difference may be due simply to the fact that we are consulted more by women than by men, who still feel some shame

in the investigation of their fertility. Furthermore, although we trust the semen analysis as one of the best ways of demonstrating fertility, we are still more comfident of our methods of examining the woman.

We agree completely with the author that hysterosalpingography is the best way to determine the patency of the tubes and is more reliable than the Rubin test. We have not been successful with surgery in the treatment of infertility of tubal origin. We have had only one case of transplantation of the ovary inside of the uterus followed by pregnancy.

It is nice to learn that artificial insemination was done only with the husbands' semen. Recently we gave our opinion that we do not consider artificial insemination with donor semen as strictly ethical. This opinion was not the result of any religious idea, but of a medical scruple. In middle class it is considered that the husband who permits his wife to be inseminated with semen other than his own exhibits a very low moral standard.

DR. WALLACE B. BRADFORD, Charlotte, N. C.—These patients are often worthy of our best efforts, although they are frequently dreaded by the busy physician to whom they sometimes seem to be time consuming and boring, not presenting enough pathology to challenge adequately his interest and skill.

It is unfair to the conscientious and cooperative infertile couple to imply that little or nothing can be done and to fail to make a proper investigation and the indicated efforts at therapy. This paper suggests that nature can often be assisted in her course.

This is not a report from a medical center or a specialized sterility clinic but rather an attempt at evaluation of results in office private practice with the type of personal and laboratory facilities that can be made available in almost any community. The figures are not comparable to the results in large groups of patients in a big city outpatient clinic where adhesive and inflammatory disease would be expected to have a higher incidence. The percentages in themselves do not mean a great deal and the criteria of sterility are not rigid enough to give this paper real statistical validity. I do believe, however, that this report lends encouragement to both patients and physicians who will concern themselves with this important field of medicine.

Original Communications

PSYCHOSOMATIC ASPECTS OF DYSMENORRHEA*

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DYSMENORRHEA refers to the physical and emotional disorders which may occur twenty-four to seventy-two hours before, or soon after the onset of the menstrual flow. In the pathogenesis of this symptom, there are two broad categories: The physical, which includes any organic disturbance that may affect the function of the sexual organs so that it leads to a lack or imbalance of the normal physiology and of the ovarian secretions. This eventually is reflected in a disturbed sexual maturity. Conversely, the emotional, which is designated by the term psychogenic factors, may influence the physiology enough to bring about significant changes. This latter effect will be the main topic of this discussion.

The symptoms of dysmenorrhea vary greatly although the same woman usually has the same group of symptoms in each dysmenorrheal state. Some women suffer from pains which resemble those of labor and discharge blood clots, and others may have an engorgement of the pelvic organs. Still others may have the typical dysmenorrheal colic. The variations and gradations of these symptoms are familiar to all of you. Associated with the physical aspects of dysmenorrhea are emotional reactions which may vary from a state of irritation and depression to a profound reaction which in many ways resembles the clinical picture of an agitated depression. Again, as in the physical response, there are variations, combinations, and gradations of symptoms which include any or all of the symptoms in the scale of emotional reactions.

With this introduction to the symptom complex of dysmenorrhea, let us turn to a consideration of the two-sided aspect which any psychosomatic approach must take into account in order that the problem be adequately delineated. Generally, there is a tendency to attempt to account for physical changes on the basis of emotional disturbances, and this is considered to be sufficient. As a result of this, only one side of the problem is approached. The other side, which poses the question, "What is the effect of a physiological disturbance on the emotional state of an individual?" is frequently neglected, but is no less pertinent to the problem. The psychosomatic approach to medicine meets its most promising challenge in investigations of the functions of the sexual apparatus. In no other field are the physiological and psychological aspects of a function so intimately related as in sexuality.

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In approaching this problem from the standpoint of the effect of a physiological disturbance on the emotional state of the individual, we have only to look on animal experimentation to see how directly a physiological lack exerts a significant influence on temperament and behavior. Castration as well as spaying has always been employed on farms to achieve temperamental changes useful in the domestication of animals. In human beings, too, the early removal of the ovaries results in hormonal insufficiencies which lead to sterility and interfere with emotional female characteristics. In the study of the integration and the maturation of any individual, psychoanalysis has discovered the importance of the maturation of the functions of the sexual glands.

Dysmenorrhea is only a manifestation of a disturbance that involves all aspects of the menstrual cycle as well as a general disturbance in the individual's personality make-up. In order to examine the interrelation of these processes more closely, it is necessary first to describe the effects of the female sexual hormones, and then to describe briefly the psychosexual maturation of the woman.

The female cycle is influenced by a complicated set of hormones interacting with each other as a balanced and rhythmic process. In the first aspect of the cycle, there is the estrogen hormone which exerts its effect on the ripening of the ovum, and in the second phase there is the progestin hormone which is important for growth of the lining of the womb so that the fertilized egg can be received, and its nourishment begun. At the time of the menstrual period there is a low level of progestin activity, and a build-up in the estrogen level. In the first half of the cycle, that is, in the stage of estrogen production, there is an associated emotional response. The woman at this time experiences a feeling of outgoingness. She is more interested in the objects in her environment. There is an increase in the aggressive feelings. Her facility in handling her routine activities is enhanced. The direction of her warm and tender feelings is outward. This is understandable in the light of the physiological function of the estrogen hormone. It is directed to preparing the organism for the ripening of the sex cells. Emotionally, too, it is directed toward the purpose of accepting a mate at the time when it would be most likely for conception to occur.

At the end of this phase the ovum is extruded and the progestin hormone begins to exert an increasing effect. Physiologically this hormone influences the mucosa of the uterus and prepares it for the reception and implantation of the fertilized egg. The emotional concomitant to this phase can best be described as a preparation for pregnancy and motherhood. The woman turns her attention and feelings onto herself. She is interested in her own bodily appearance. This is expressed best in concern about her clothes, her hair, and so on. There is an emergence of passive receptive feelings as opposed to the former aggressive ones. A kind of placidity pervades the woman, and her fantasies may be actively concerned with thoughts of pregnancy and the love and care of children. Again, we see the correlation of the physiological function of a hormone with its concomitant effect on the individual's emotional life.

If pregnancy has not taken place, the production of progestin diminishes, and before the menstrual period the quantity of sexual hormones is at its lowest. This is reflected also in the emotional life of the woman. In this premenstrual phase, the woman may feel and act less composed. She may be irritable and moody. She may be more aggressive or more dependent. There is a general feeling of a lack which is actually a response to an imbalance or the low level of hormones in the body. In the pathological states this may be expressed in the symptoms associated with dysmenorrhea.

In describing the effects of the physiological processes on the emotional state of the individual, the following two factors must be kept in mind. (1) These changes are not as sharply defined and abrupt as would appear from the description. The physiological changes are subtle, and though at one point a specific hormone may be in predominance, it is also true that the other hormone or hormones are still present and exerting their effect. (2) The hormone is to be regarded not as a stimulus to behavior or as an organizer of the overt response, but merely as a facilitating agent which increases the reactivity of the specific neuromuscular system to stimulation. In a manner of speaking, it acts as a catalyst to behavior.

Now let us approach the problem from the other side of the coin. How can the emotional structure of the individual influence the physiological reactions? It is not within the scope of this discussion to examine in detail the psychosexual development of the personality. For the sake of clarification, it is necessary to examine at least the concept of psychosexuality so that its role in influencing the behavior of the individual can be understood. This concept holds that within the first six years of an individual's life, the basic patterns of reactions are laid down. These reactions include the relationship to members of both sexes. The prototypes for these relationships are the reactions and their emotional equivalents which have been felt toward mother, father, and siblings. Roughly, this period is divided into two categories, the pregenital and the genital. Since the focus of this discussion is mainly on the genital period, it is sufficient to state briefly that the pregenital period is concerned with the early feeding phase of the child, and the bowel-training period. These, of course, influence directly the attitudes and emotional responses in the genital phase.

In the genital phase, the girl has for the first time to test her sexual feelings as they relate to the father as a sexual object and as to mother as a competitor. It takes this struggle in the oedipal period to measure the degree to which the girl will take risks in the direction of a heterosexual development or the tendency to recoil from it because of the strength of the opposite tendencies. Normally the direction is toward the heterosexual development, and the girl later in life with the upsurge of the endocrine production at puberty is able to acept her role as a woman. This essentially includes the ability to be a wife and mother.

In the case where the strength of the opposite tendencies remain dominant, the result is quite different. These opposite tendencies are present for

many reasons, among which may be guilt over incestuous desires toward father, hostile or dependent feelings toward mother, or guilt over sibling rivalry. This can be elaborated with endless variations, but its importance lies in the fact that, in the developmental phase, the meaning of motherhood and wifeliness has become distorted and endowed with fearsome prospects. The distortions and the fears have been brought about through the disturbed relationships with the parents and siblings. These, though they may be varied and complex, tend in a general way to increase the masculine identifications and this reinforces the bisexual tendencies of the girl.

With the onset of puberty and the subsequent adolescence, the problems which have remained dormant and unsolved during the latency period are reawakened by the upsurge of the ovarian secretions. This results in the disquieting symptoms of development which constitute the characteristics of the period of adolescence. The severity of the adolescent conflict is determined by two psychodynamic components: the intensity of the instinctual need produced by the physiological stimulation and the degree to which the girl has remained fixed in the direction of her bisexual tendencies, that is, the individual's inability to go in the direction of her heterosexual strivings. The energies that would be utilized in the direction of the functionally mature woman are partially spent in conflictual processes. Thus, there is a complete or partial loss of the energy. Accordingly, it appears that not the production of sexual energy but the way in which it is spent accounts for the variations in sexual behavior in women. The sexual cycle recreates at rhythmic intervals the problems which have been inadequately resolved during the individual's development. In the premenstrual and earlier menstrual phase, the low ovarian function, plus the increase in the general irritability of the nervous system, creates a tendency away from the integrating heterosexual drive. The resultant increase in symptoms of irritability and depression may account for the fact that this phase is often described as the recurrent neurosis of women.

With this sketchy outline of the development of the sexual functions as an inter-reaction between the psychosexual development on the one hand and the physiological development on the other, let us turn to the examination of the symptom complex of dysmenorrhea and examine it in the light of these two aspects of development.

First, let us discuss the physiological effect of menstruation on the emotional make-up of the individual. From the earliest times of which we have record, the menstrual period in women has been surrounded with ideas of horror—danger and fear of the contamination in the mind of others, and with shame and guilt on the part of the woman herself. These primitive beliefs and feelings have inevitably led to the institution of strict taboos, and an endless number of strange superstitions and anxieties. In general, the taboos related to the segregation of menstruating women are related to the harmful effect which might accrue from her contact with any productive activity of the family or group. The primitives reacted as though there was a "blighting" aspect to her personality at this time. How much of this remains in our present

civilization is easily answered if we investigate the ideas of the more backward people. However, even in our more urban communities where supposedly there is no conscious awareness of our primitive notions concerning menstruation, there is still the obvious reference to it in the common expression used to signify menstruation—the curse. At the same time we may find many of the older theories, which in general have become obsolete in the conscious mind of our contemporaries, continuing to survive among the dreams and phantasies of persons whom one has had the opportunity to investigate during psychoanalytic treatment. Is it any wonder, then, with these attitudes and reactions which exist in relation to a normal physiological process, that 40 to 50 per cent of the women of today suffer from some form of menstrual disturbance?

The woman of today grows up in a culture which on the one hand prides itself on its liberal approach to sexual problems and yet on the other hand continues to respond to a normal physiological process, if not openly, at least by inference, with feelings and attitudes that bear the stamp of a much more primitive culture. In the cycle which this produces, the girl is first made aware of the taboos, anxieties, fears, and dreads that anticipate the first menstrual period. The onset of menstruation may come as a surprise or shock, or be surrounded with anxiety. Any physiological disturbance which may manifest itself in the laying down of any physiological pattern can create discomfort for which the girl stands prepared with her anxieties to trigger a reaction which brings on the first dysmenorrheal syndrome. This is reacted to with the anticipatory fear of the pain of the next menstrual period. Already the anxiety has found a point of fixation. The vicious circle is set up and continues until some fortuitous situation of reality or some kind and understanding physician can help the woman reorganize her emotional attitude toward her menstrual periods.

This describes a possible reaction to a normal physiological process. What about disturbed physiology on an organic basis? The decrease or dysfunction in ovarian secretions creates a lack of the important facilitators of behavior. This makes it more difficult for the woman to reach a level of emotional integration that would help to sustain acceptance of her role in life. The conflict is not aided in its direction toward a more integrated solution, and so the regressive tendencies are more dominant. The resultant anxieties on an emotional level, and the increased excitability of the nervous system which has been brought about by the decreased ovarian function, predispose the woman to an over-reaction at the beginning of the menstrual period.

Finally, let us turn to a discussion of the influence of emotional factors on the physiological processes. As in any psychosomatic discussion, the final problem, and always the problem most difficult if not impossible to answer, is the channels by which the psychological disturbance is carried from its origin in the central nervous system to the end effectors in the organ or organs under consideration. I take this up first in order to dispose of it so that the psychogenic factors can be approached without asking ourselves the difficult question, "How does it work?"

Perhaps the most illuminating description, and also probably the most controversial one, is that of Benedek and Rubenstein. In their work on the menstrual cycle in the woman, they claimed that they could detect from the patient's dreams and other evidences of unconscious activity the amount of progesterone and estrogen that was being secreted by the ovary. They felt that in their neurotic patients the emotional reaction had a direct effect upon the level of ovarian hormone secretion, and that the disturbance in secretion resulted in the symptoms. Later, Benedek elaborated on this, and stated, "Dysmenorrhea, although it represents a reaction to deficient (infantile type) ovarian function, is not a symptom of hyposexuality alone. Rather, it is a result of the diminishing control of the ego over the psychosexual conflicts." This also is inadequate as an explanation of how the end organs are affected. The list of pathways by which the end organs are finally reached takes up a few chapters in our recent research in psychosomatic medicine. Suffice it to say that in addition to the endocrine factor which in itself is quite controversial, there are theories which include heightened sensitivity of the nervous system, changes in the tissues' capacity to retain sodium with subsequent increase in water retention, changes in the autonomic system, as well as changes in the biochemical and physiological states. All these theories only indicate our present lack of knowledge and technical development. Probably all of these factors are in some way intimately related, and future study will have to give us the answer.

The emotional conflicts which are related to dysmenorrhea are not specific to the symptom complex itself. Just as dysmenorrhea reflects a disturbance that is related to the rest of the sexual cycle, and just as dysmenorrhea may take different symptom-complex formations, so it is that the emotional problem involves all of the aspects of the woman's personality, and that one woman's conflict may have a different character from that of another woman. The basic conflicts are reached only through a long psychoanalytic procedure and are specific for each individual.

In general, however, there is a similarity in the emotional structure of these women. Menstruation has a definite meaning for all women. It is their badge of womanhood. The degree to which that badge can be accepted will depend upon the unconscious attitudes toward femininity which become an integral part of the woman's personality in her psychosexual development. These early situational experiences may be as variable as there are women with dysmenorrhea, but in general they reflect a tendency which pulls toward the more regressive bisexual response and away from the more mature heterosexual development. As examples of these forces we have early oral fixation which translated into behavior attitudes means that the girl cannot give up her relationship with the mother, but must cling to her as a child. Any approach to a mature sexual relationship threatens the woman's childlike relationship to the mother. The role of a woman and of a mother becomes a threat and is filled with anxieties and dreads. Menstruation, which is equivalent to being a woman, becomes a nightmare which this woman must relive at monthly intervals.

Other early experiences which bring about a similar response include a poor relationship with the father, either in the form of rejection from the father on a seductive relationship with him. Any strong feelings of rivalry with other siblings, especially brothers, will stir up feelings in future close relationships to a man which will contain the past elements of hatred, revenge, feelings of inferiority, as well as a threat to the dependent relationship to mother. Here again the direction is away from the acceptance of the feminine role. All these feelings mobilized at the time of menstruation are reflected in its concurrent symptoms.

Perhaps a brief case history will be most helpful in illuminating the general components involved in this problem.

This 24-year-old unmarried girl came to treatment because of severe anxiety and vomiting which came at the time of menstruation and were associated with dysmenorrhea. This patient had been symptom free until the age of 20. At this time she had an important date with a man toward whom, for the first time, she felt a significant interest and affection. The party ended with a late night snack. It was then that she experienced her first intense anxiety and nausea. At the next menstrual period, the premenstrual tension was markedly increased and was associated with nausea, gagging, vomiting, and the start of severe premenstrual cramping. These symptoms recurred with each subsequent menstrual period.

This woman was the first of two siblings. The other sibling was a brother who was two and one-half years her junior, and who was the mother's favorite. The parents were divorced when the patient was 6 years of age, and there was an interval of one and one-half years before the patient saw her father again. In her subsequent relationship to her parents, she felt the intense need for her mother which she tried to deny by pseudo-independent rebellious behavior which helped only to increase the need. The menarche was handled by the mother with the not too unusual approach of many mothers which consisted in leaving a book in an obvious location so that the girl could become aware of "What Every Young Girl Should Know."

This skeletal case history will suffice for purposes of illustration. From this description the earliest relationship to the mother was first threatened by the birth of her brother. The competitiveness with him is obvious in much of the material. The mother's preference for the son is already the first obvious pull away from the feminine identification. Put in the child's simple terms: "It is better to be a boy in order to be loved by mother." The subsequent divorce of the parents at a time when the patient was testing her relationship to her father in the light of her feminine tendencies could mean to the child that in any relationship to a man she would be rejected. Father left at a time when she was relating to him with the most intensive feelings. The child reacted to the divorce as a personal rejection, and as a rejection of those very tender feelings.

Following this the child turned back to the relationship to mother, in a more intense and profound way than before. The stage was set then for the onset of the dysmenorrhea the first time the girl re-experienced those feelings which in a previous situation had proved so painful and traumatic to her. In the first stirrings of those feelings in relationship to a man at the age of 20, the old anxieties, fears, anger, and rejections were once again mobilized. The patient's response to these overwhelming feelings was to protect herself with

her symptoms. The need to deny her feminine identity, to revert to earlier modes of behavior which brought her into a closer relationship to mother were all laid down in the earlier life experiences which have come to shape her present dilemma. The menstrual period becomes an additional threat which exposes her basic biological make-up. The stirring of her sexual feelings becomes the ultimate threat that revives all the old experiences.

It must be kept in mind that this case is one where the pathology is quite profound, and the symptoms are then much more overt and intense. In many cases, this will not be as obvious. The character defenses of many of these women are much more adequate so that on the surface it may seem that they are apparently emotionally mature. In a sense, they are. They have certain successful ego defenses which allow them to function well in their family and social relationships. It is only after talking to them for some time that one can discover the same general trends. That is, the rejection or partial rejection of the feminine role, and the early more regressive attitudes toward their environment.

Last, I would like to point out something that has already become obvious from this discussion. Psychoanalysis has certainly not discovered all the answers. This science which has so very recently come into its own is struggling with the problem of etiology in terms of attempting to discover the elements involved in the choice of the illness. Specificity of disease as related to the emotional conflict is a problem that awaits its answer in the perfection of more adequate techniques that will allow for a more microscopic approach to the patient's problems. Medicine, too, finds its limitations in the limitations of physiology, biochemistry, and the other related laboratory techniques. The gap between the emotional conflict on the one side and the physiological response on the other is the focus of the future answer to the present enigmas. As we become more conversant with the emotional structure of the individual, and as you, as clinicians, discover more of the physiological biochemical, and neurophysiological pathways over which these emotional conflicts are carried to the end organs, then the obvious gaps which are so confusing will become narrowed and finally bridged.

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SECONDARY DYSMENORRHEA*

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SECONDARY dysmenorrhea is due to various abnormal conditions within and without the generative tract. It can be differentiated from the primary type of dysmenorrhea in most cases rather easily by the nature of the pain which is more likely to be of a dull aching character but which persists as a rule through the period and gradually disappears after the flow has ceased.

It is also possible to demonstrate rather easily the pathological conditions on which it depends and whose correction results in the disappearance of the symptoms. Pelvic congestion and chronic inflammation have been stated by most authors to be the immediate cause of the pain. It must, however, be remembered that in addition to these factors one must not overlook the fact that many of the patients suffering from primary dysmenorrhea may in addition develop conditions which will produce secondary dysmenorrhea. Obviously in such cases the removal of the secondary causes of dysmenorrhea would not cure the patient and if complete relief had been promised by the medical attendant she would be greatly disappointed in the outcome of his management. This mistake can be obviated only by careful assay of the history given by these patients, noting particularly the time at which dysmenorrhea first appeared, its character, and the changes in the type of pain from the colicky primary type to an associated dull aching type of pain which in general lasts longer and disappears more slowly after menstruation.

The relationship of secondary dysmenorrhea to the psychosomatic concept of dysmenorrhea will be covered by Dr. Robbins. I may say, however, in this connection, that the effect of lesions in the pelvis which may produce secondary dysmenorrhea due to local pressure from congestion also have a profound effect on the mental processes of the patient, especially those patients who may have a bad family history as regards the incidence of carcinoma. It has been my observation that when these patients can be assured that their pelvic pain is in no way related to malignant disease much of their dysmenorrhea, if not all, will disappear.

Ovarian pathology is not infrequently associated with dysmenorrhea. We have observed various forms. Small cystic ovaries of the follicular type are frequently tender and are also associated with sterility. Wedge resection of such ovaries as pointed out by Stein frequently results in normal follicle development and cure of the sterility, and also we have observed improvement in those cases in which dysmenorrhea has been a complaint.

Another form of dysmenorrhea has been associated with anovulatory menstruation and the ovaries in many of these cases are relatively small and

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sclerotic with a markedly thickened yellowish capsule. We have resected portions of these ovaries in the hope that the symptom of dysmenorrhea could be improved, without much success.

Salpingitis, subacute and chronic, and tubovarian abscess are almost always associated with dysmenorrhea. The pathology is easily detectable except in very obese patients and improvement follows medical management. Failure of improvement after reasonable trial of medical management or repeated recurrence of acute exacerbations calls for surgical removal. In this connection the dysmenorrhea associated with unilateral right-sided tubovaritis should be carefully followed and explored if the dysmenorrhea does not improve and the local findings progress, because of the danger that the inflammatory processes involving the adnexa may be due to actinomycosis. The eradication of this disease depends on its early recognition and intensive treatment.

One of the most important forms of secondary dysmenorrhea is that associated with endometriosis. The well-known tendency for the pain to appear previous to menstruation by two or three days and disappear or become much better following the onset of the flow is common knowledge. Also, it should be stated that this condition is much more common in women in the late twenties or early thirties. In occasional cases, however, the fact that it occurs in younger women and in those in whom the dysmenorrhea does not develop until after the flow starts may be overlooked. I should like to call attention also to the fact that in those patients in whom endometriosis involves the rectum and bladder, not infrequently symptoms of bowel irritability and dysuria occur, especially at the time of menstruation.

Dysmenorrhea associated with adenomyosis is usually associated with an enlargement of the uterus and a progressive menorrhagia. However, the dysmenorrhea may precede the gross changes in the uterus by some months or years. We always observe these patients carefully for other evidence of pelvic endometriosis.

Dysmenorrhea associated with fibroids is a common finding in our clinic and is probably chiefly due to the increase in the size of the uterus at the menstrual period. Also the tendency of menstrual blood to clot in the fibroid uterus may increase the pain produced by the congestion and give rise to colicky pain produced by uterine contractions necessary for the expulsion of these clots. We have also noted that fibroid uteri which do not have much dysmenorrhea may develop this symptom suddenly. When this occurs we believe that it is strongly suggestive of a hemorrhage or vascular accident within the fibroid. This may have a bearing on our decision as to the management of that particular case.

Another form of dysmenorrhea which occurs in the fibroid uterus is that secondary to a submucous fibroid. These cases are usually associated with menorrhagia and the pain may be crampy like a labor pain due to attempts of the uterus to expel the fibroid. Cervical fibroids may by impinging on the cervical canal result in stenosis of the canal causing dysmenorrhea.

Chronic cervicitis with associated lymphangitis of the uterosacral ligaments also may be associated with dysmenorrhea. In such cases the stricture is usually

easily demonstrated by the passage of a fine probe in the interior of the uterus and likewise distortions due to fibroids can be readily detected.

One of the most common causes of pelvic pain and one which has received scant attention from the gynecologist is sacral nerve-root neuritis. Women who are subject to this condition may have an exacerbation of and discomfort associated with the congestion which occurs at time of menstruation. This lesion is not difficult to diagnose. These nerve roots lie on the side wall of the pelvis after emerging from the sacral nerve root canal and come together to form the sciatic nerve. Digital pressure on these nerve roots readily reproduces the pelvic pain of which they complain and frequently this pain radiates down the leg and may be associated with numbness of the leg and foot of the affected side. It is frequently bilateral, much easier to diagnose than to cure. Treatment must be directed to the detection of the cause of the neuritis and its elimination if possible.

Secondary dysmenorrhea may be associated with lesions of the urinary tract. Chronic cystitis and abnormalities of the ureter should be suspected when dysmenorrhea is associated with urinary symptoms and ureteral colic during menstruation.

In such cases careful cystoscopy and catheterization of the ureters together with pyelograms will usually demonstrate the urological complication responsible for the symptoms and if it can be removed the symptoms will be relieved.

Tuberculosis involving the pelvic organs not infrequently will be first noticed when the patient begins to complain of dysmenorrhea. Local tenderness, low-grade fever, weakness and weight loss, a doughy consistency of the abdomen with postprandial pain combine to form a characteristic picture, especially when supplemented by ascites. It is assumed the increased tension on the inflamed peritoneum incident to the menstrual congestion is responsible for the dysmenorrhea.

Uterine displacements especially retroversions seem to have an important bearing on dysmenorrhea in some cases and none at all in others. However, it is simple and logical to replace the uterus and support it with a pessary (when the uterus is freely movable) in order to determine whether or not the displacement is the cause of the symptom. Once this is determined the advisability of more permanent correction can be determined according to the circumstances surrounding the case.

Cervical lesions seem to be responsible for a considerable number of dysmenorrhea cases. Chronic cervicitis draining into the lymphatics of the uterosacral ligaments causes them to be acutely tender to palpation. Menstrual congestion likewise produces backache and pelvic discomfort. In chronic cases Sturmdorf conization, removing a large percentage of the chronically infected glands, frequently cures the dysmenorrhea. Cervical stricture, congenital or acquired, also may play a role in dysmenorrhea usually due to the retention of blood clots within the uterus necessitating strong contractions for their expulsion. Thorough dilatation in such cases often has a curative effect which may be temporary or permanent depending on whether the stricture re-forms. This is the group which derive the greatest benefit following delivery.

A curious form of dysmenorrhea may occur in patients with rudimentary uteri and adnexa, and absence of vagina. In these cases even though there is no attempt to menstruate the women complain of cramp pain at regular intervals. The best explanation is that it is due to autosuggestion since I have seen no physical findings in patients operated on to explain the symptoms.

Discussion on Symposium* on Dysmenorrhea

DR. EDWARD ALLEN.—I wish to give a few results from our study of a third group of the nurses from the standpoint of dysmenorrhea and mention again two or three angles that the other essayists have mentioned.

This group has been studied from 1948 to 1952 and consisted of 443 nurses, 17 to 22 years of age, living under the same conditions and doing the same kind of work. I want to give you the interpretation of the nurses in charge as they studied this and commented on it. I think it is an important problem, in which the most valuable thing was the days lost. In 1948, it was found that there were 13 days lost; in 1949, 19 days; 1950, 44½ days; 1951, 79; 1952, 109½, which makes a total of 265 nursing days lost, so our treatment is not working very well.

It was found that 80 per cent of these girls developed their dysmenorrhea after entering training. I think that is an important item. When we looked over these girls some time ago we found that their main trouble came when they worked in the operating room, in the maternity room, and in the delivery room. It was believed that was due to the intense tension in the operating room and delivery room.

A further analysis of this group showed that this 80 per cent increase in dysmenorrhea was in those girls who went to the Illinois Neuropsychiatric Unit which is affiliated with us for training. They made the observation that much of this increase in dysmenorrhea and time lost was due to the desire to escape disagreeable duty. We have checked a goodly number of those who asked for morning hours and were so uncomfortable that they could not go out with the duty assigned to them, and yet that evening they went to one of the nurses' dances and had a very good time.

I wonder as we analyze the essential or primary dysmenorrhea, if we could not look well at what occurs in the normal young woman who has cramps, gets married, and is relieved. Quite a number are relieved by marriage, but the vast majority of them are cured by pregnancy. Is that due to just simple dilatation of the cervix or is it a change in the nutrition and glandular balances that occur during the period of pregnancy?

Thirty-five per cent of these nurses who had disturbed physiology were off the nutritional standard enough to call them abnormal. I am sure that any of you who treat amenorrhea, menorrhagia, or any of the other functional diseases and have previously been giving hormones or other medication have seen them recover by loss or gain of adequate weight.

I have not had the results reported this evening with estrogen and testosterone. In my hands dilatation has worked almost as efficiently as these drugs. One of the nurses in this group had such severe dysmenorrhea that she admitted taking narcotics. She met a medical student and had been married six months. When I saw her again she was quite comfortable at period time. Her husband had increased her thyroid therapy from one to two grains daily with prompt relief. In our experience thyroid is the most effective hormone in the treatment of not only the nutritional disturbances but those functional disturbances associated with amenorrhea and menorrhagia.

I am not quite scientific enough to know about the so-called anovulatory periods. I have seen several of these young women who have been told their troubles were anovulatory and we dilated several of them and opened the cul-de-sac to find a nice ripe corpus luteum.

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*Psychosomatic Aspects of Dysmenorrhea by Fred P. Robbins, M.D., page 808.
Secondary Dysmenorrhea by Frederick H. Falls, M.D., page 816.

We believe the stem pessary should not be used on account of the tendency to set up a chronic infection. In dilation the results we get are probably not just due to making the canal larger but to some mechanical response that is similar to that of the dilatation of the cervix by pregnancy and delivery, the use of douches, or trauma to the ovaries.

It seems to me that early training of the adolescent girl has much to do with the appearance and persistence of dysmenorrhea. We are all aware of the effect of fear and training on the severity of labor pains. A sane, sensible approach to the physiological meaning of menstruation would cause less rejection by the female than we see so frequently.

DR. ERNEST M. SOLOMON.—There is perhaps no field of medical endeavor, short of psychiatry itself, which demands more objective understanding of, or insight into, the patient's emotional status or personality equivalents than the practice of obstetrics and gynecology. This has long been recognized. In my library there is a book entitled *Gooch on Females,* published in 1832. Dr. Gooch was physician at St. Bartholomew's in London. He writes of dysmenorrhea as a disease of function, suggests a morbid connection of the nerves, and that its occurrence is chiefly among hysterical females. Unfortunately, his therapy consisted in blood letting and blistering the skin of the sacral area.

James Henry Bennet, writing in 1852, speaks of functional derangement and nervous susceptibility.

In 1896 Wells of the Philadelphia Polyclinic described "neuralgic dysmenorrhea" in patients with a general neuralgic diathesis. And so it has always gone, and so it will continue.

Modern textbooks of gynecology refer to the emotional or psychosomatic aspects of dysmenorrhea, although they give varying degrees of weight to this factor. Curtis and Huffman refer to a nervous temperament as being a factor, but pray that we do not overemphasize the neuroses in our evaluation of this syndrome. Brewer, on the other hand, unequivocally states that psychogenic causes are the most common and the most important in women with primary or essential dysmenorrhea. He further urges that some form of psychotherapy be the basis of management.

Mazer and Israel place this symptom complex in the realm of constitutional disorders of the autonomic nervous system, and advise a careful investigation of the emotional status of the patient along with physical investigation.

Thus all give at least lip service to the psychic aspects of the problem; many give a good deal more. I agree with Dr. Brewer that it is incumbent upon us to investigate further an avenue of approach that dynamic psychiatry has opened progressively for us in the recent decades.

Dr. Robbins' paper is an opportunity to hear from and discuss with the psychiatrists what they have learned. It is an excellent presentation and to the point without detracting in any way from our organic investigations. Indeed, it must be a combination of the two methods of inquiry which will eventually give the answer in so far as the mechanism of psychic effect on somatic response is concerned. But even before this question is answered, we have available to us from the kind of information Dr. Robbins has presented a clue to the therapy of these unhappy individuals.

Recent reports gave us hope that endocrine therapy might be useful. All too often it is not, and when successful it is only symptomatic and temporary therapy at best. The immediate problem then is not so much to understand that hormonal titer or lack of it can be an activator of abnormal emotional states, although to know this is helpful; rather, the problem is to understand the enormous variation in response to the activating or catalytic stimulus, i.e., why there is minimal or no response in one woman, and perhaps a severely abnormal response in another up to the point of prostrating dysmenorrhea. But to alter, i.e., to correct, abnormal emotional stimuli, offers real and lasting hope. It is obvious that this is no easy trick. That the bisexual conflict with modifying overtones is basic in the problem I am able to accept. Also that it has its origins in early life experiences. But we are not and cannot be trained psychiatrists and gynecologists at one and the same time. Further, we cannot, nor would we wish to refer all such problems to the psychiatrist. Hence,

we are forced into some form of homespun psychiatry which perhaps is the essence of the art of medicine. There is no reason why this should not be so, and our hope is for more and more enlightenment on the dynamics of the unconscious mind. We are forced to recognize that chronological age and outward appearance are no evidence of true maturity. Our patients all represent varying degrees of acceptance of the role of maturity and of womanhood, varying degees of conflict concerning this, and varying degrees of control of these problems.

In so far as can be determined by first carefully ruling out organic pathology, it has been my experience, small as it is, that patient explanation, understanding, and acceptance plus minimal symptomatic therapy are worth more than hormones or instrumental manipulation. Time spent with these patients at a level of complete acceptance of their problems and their personality is well invested. Many will recognize sympathetic understanding and respond to it, and can be brought to a more comfortable acceptance of their feminine role, and of menstruation as a symbol of it.

It has been of interest to me that the vast majority of patients with essential dysmenorrhea are the outward epitome of femininity. Clothes, mannerisms, behavior, etc., are openly feminine and often provocatively so. Perhaps Dr. Robbins will explain this. It is also of interest that though, as the essayists remind us, menstruation is commonly called the "curse," the absence of it with pregnancy ruled out is a common cause of extreme anxiety. Would Dr. Robbins agree that this as much as anything demonstrates conflict over the feminine role; the same conflict that produces abnormal somatic reactions one of which may be dysmenorrhea?

Another question that occurs to me concerns the patient who has dysmenorrhea of this type every other month. Is this bimonthly ovulation, and if so how can we account for such a constant reaction to the hormone activator if the emotional status is primarily at fault? No conflict, even in the unconscious should be at a constant level of pressure. Many such questions will obviously arise as we inquire further into this problem.

I hope that Dr. Robbins will give us a "modus operandi." From a technical standpoint are there any basic principles he can give us for our homespun psychiatric handling of these patients? It seems that all too often our efforts at therapy tend to increase the patient's fixation on her genitals as the somatic solution to her problems. It is now up to the psychiatrists to add to our "know how" in the treatment of functional dysmenorrhea.

DR. RALPH A. REIS.—May I emphasize one thing which I did not hear mentioned tonight, something that Edward Allen emphasized so beautifully ten or fifteen years ago, that is, before we treat these girls for primary, secondary, or tertiary dysmenorrhea to examine them carefully per vaginam. I still see many girls who have been treated one way or another and who have never had a vaginal examination.

DR. ROY R. GRINKER.—Dr. Robbins has presented an extremely succinct and easily understandable explanation of the psychosomatic aspects of the most common gynecological problems. The menstrual cycle is such a universal and repetitive process in women that it becomes an easy means of representing a great many various kinds of emotional disturbances. Within this cycle women may project many of their emotional problems. Menstrual difficulties, therefore, not only represent disturbances of many hormonal processes but also of many psychological problems. So many variables conjoin to make the menstrual cycle that it becomes difficult to determine which factors are of greatest significance.

It is not well enough understood that there is a difference between pain and suffering. Pain is a physiological process conveyed over known neural pathways but it is quite often independent of the psychological feeling which is called suffering. Each individual has his own kind of emotional reaction to pain and his own quantitative threshold. Some of you know that after lobotomy the patient does not suffer pain but has all the normal functions of responding to pain as before. In the field of dysmenorrhea we have the problem of the subjective suffering and the difficulty of differentiating it from the actual pain due to mechanical processes. In cases of suffering cutting the nerve supply will have little effect for the suffering then will be attached to some other organ or even continue in relation to the organ that was denervated.

Dr. Robbin .as shown very nicely that there are various levels of psychological disturbances that can be expressed in relation to the menstrual cycle. Some of these which he has accentuated are fear of pregnancy or fear of lack of pregnancy or difficulty in assuming the feminine role. Although these anxieties may have been present for many years at the time of the beginning of menstruation, they may be attached to the menstrual process itself. There are no simple ways by which we can disentangle these multiple factors. One thing we are sure of, and that is, whether the process begins as a psychological disturbance or as a hormonal imbalance, both psychological and physiological systems will be involved. There is no limitation to one aspect of the problem. This has necessitated the comprehensive or psychosomatic point of view.

Tonight there have been presented many kinds of treatment suggested to help the patient with dysmenorrhea. I should like to suggest that the treatment not be viewed as a specific by itself. So many things can be given to the patient and so many manipulations can be brought about, each one of which has the same result, that I think we should look into some other facet of the therapeutic process. I think that we should look not at the instrument or the drug that the doctor holds in his hand or prescribes but in the relationship that exists between the doctor and the patient. The emotional factors which exist between the patient and the physician are independent of the knife or the medication.

This means that the therapeutic process itself although disguised by a physical method is nevertheless psychological. I think that Dr. Solomon has pointed out very accurately that you cannot send all your dysmenorrhea patients to psychiatrists as certainly the psychiatrists cannot handle them all. The gynecologist, however, can treat his patient with a mind as open as possible to the psychological implications of her suffering. This requires the attitude of a patient listener who attempts to unravel the emotional problems and the life situations as they may be significant in producing the suffering. The gynecologist needs to examine not only the pelvic organs but also the processes of communication that the patient is eager for him to receive. With a modicum of time and understanding one can determine what are the problems of each individual and know which ones require certain attitudes, reassurances, or reinvestigations. For this the gynecologist need not be a psychiatric expert but he can be as good as any psychiatrist if he attempts to let his feelings respond to the feelings of his patient.

THE TREATMENT OF FEMALE GENITAL TUBERCULOSIS WITH STREPTOMYCIN AND PARA-AMINOSALICYLIC ACID

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THE treatment of genital tuberculosis until recently was limited to the employment of sanatorium care; the use of operative measures by which an attempt was made to remove partially or completely the tuberculous lesion; or the utilization of a combination of both procedures.

In 1938 Rich and Follis[1] first noted experimentally that sulfanilamide exerted "a striking inhibitory effect on the development of tuberculosis in the guinea pig." This report suggested that the old hypothesis, "the tubercle bacillus is peculiarly immune to drug therapy," was no longer tenable. Further impetus toward tuberculosis therapy was provided in 1940 by the Mayo Clinic,[2] when they revealed that the sulfones acted slowly, especially in acute cases, and when given in moderate or large doses caused severe secondary anemia due to hemolysis.[3] These disadvantages, however, served only to stimulate further efforts to find more suitable drugs to devitalize the tubercle bacillus in vivo.

In 1944 streptomycin was introduced and found capable of marked bacteriostatic and possible bactericidal effects against the human strain of *Mycobacterium tuberculosis*.[4, 5] For the first time in history an antibacterial agent was found which could be used safely and for long enough periods, in many instances, to be lifesaving. Shortly thereafter dihydrostreptomycin was presented as a less toxic though equally effective drug. Clinical reports, however, soon began to reveal that with both medications not only the vestibular apparatus and the eighth cranial nerve were affected, but also allergic reactions were easily induced, especially if large doses were used. A final and most serious complication was the discovery that resistant forms of the tubercle bacillus were noted. It has been variously reported that if a patient was able to tolerate 1 to 2 Gm. of streptomycin (or dihydrostreptomycin) for 120 days, resistant strains will develop in about 80 per cent of the cases. This relatively brief period of sensitivity therefore became of paramount importance because it limited the safe interval for possible surgical intervention.

It appeared as though the answer to these shortcomings, at least in part, was the advent of para-aminosalicylic acid (henceforth referred to as PAS) in 1946-1947.[6] Results have indicated that PAS is of value in tuberculosis either when used alone or, more especially, when administered in combination with

other tuberculostatic agents such as the streptomycin group. It has been well established that *its major usefulness* in combined therapy is to delay emergence of organisms resistant to streptomycin.

Our experience with the use of streptomycin in the treatment of genital tuberculosis has been reported elsewhere.[7, 8] This report concerns the *combined use* of PAS and dihydrostreptomycin in the treatment of 18 consecutive cases of genital tuberculosis. In this series of patients we wished to determine by the use of combined therapy whether or not surgery could be eliminated in the treatment of genital tuberculosis.

Dosage of PAS and Dihydrostreptomycin

In our previous work, we found it suitable and practical to use 1 Gm. of streptomycin per day in a single injection. Although PAS may be given intravenously, intramuscularly, or orally, the latter route is preferred. PAS is best given as enteric-coated tablets, because of its bitter taste. The standardized tablet is 7½ grains. The recommended daily dose of PAS is 10 to 15 Gm.[9] We have found in this small series that 12 to 15 Gm. is in excess of what the average patient will tolerate for any sufficient length of time. Experience indicates that when PAS is used with streptomycin, the maximum daily dose should be 10 Gm. If side reactions appear, the apparent minimal effective dose (MED) of PAS is 5 Gm. per day.[10] If necessary, the drug may be stopped for several days and then restarted at the aforementioned 5 Gm. daily dose.

Duration of Treatment

If the patient tolerates both drugs, they may be given for equal periods. PAS may be given in the recommended dosage, safely and freely, for 4 to 5 months. Wolskel and Barnett[11] have given PAS for as long as 9 months. Streptomycin per se should not be given beyond a period of 120 days, because resistant forms begin to appear in about 80 per cent of the cases. If combined with PAS, a 1 Gm. per day dose may be given as long as 4 to 5 months. *Our objective has been to give both drugs for as long a period as possible in an attempt to enhance the patient's own power of recovery and thereby avoid surgery.* If surgery does become necessary, it is preferred that the combined medication be continued for at least 2 to 3 weeks postoperatively. This group of 18 patients received combined therapy preoperatively, on the average of 3½ to 4 months. Those who responded favorably and were not subject to surgery received the drug over similar periods, though in 2 instances PAS was administered for 6 and 9 months, respectively, with no apparent complications.

Toxicity of PAS and Dihydrostreptomycin

Each drug, if given alone and in large enough concentrations, is capable of producing toxic reactions. Those caused by streptomycin have been frequently reported and warrant no repetition at this time. May we stress again, however, that toxic phenomena with the streptomycin group are more

likely to be encountered in patients with altered kidney function, or in those who received large doses (over 1 Gm. per day) over prolonged periods of time.

The side reactions and toxic behavior of PAS merit further discussion. PAS is readily absorbed from the gastrointestinal tract. Following a single oral dose, blood levels of the drug reach a peak within the first or second hour after administration. By the end of 4 hours, the blood levels are reduced to a minimum. Approximately 85 per cent of the amount ingested will be excreted in the urine within the first 10 to 12 hours after administration.[12]

Orally administered PAS may cause gastrointestinal disturbances. Among these are: nausea, with or without vomiting; loss of appetite; weight loss; epigastric discomfort; and diarrhea. Several patients have commented on the fact that while receiving PAS they had up to 4 bowel movements in the morning, but none for the remainder of the day. The stools were described as soft but not mushy or watery. Among other side effects noted by ourselves and others to date have been: moderate to severe febrile reactions; erythema; itching, either focal or generalized; hypoprothrombinemia, transient renal impairment, and severe leukopenia.[13] No instance of permanent hemopoietic damage, however, has been noted.

PAS has been given intravenously when streptomycin and PAS administered orally have proved ineffective. Up to 15 Gm. of PAS may be given over a period of 12 hours or longer.[14] If intravenous perfusions are not possible, then subcutaneous perfusions may be used. Thus far we have found no need to use these routes. If utilized, one should be on the alert for tetany or tetany-like crises.[15] These reactions may occur during or after the perfusion. Ten c.c. of calcium gluconate should always be ready at the bedside. It should be noted that gastrointestinal upsets seem to be the result of local effects. The parenteral administration of the sodium salt of PAS does not produce this type of toxicity.[16]

Once side reactions or toxicity appear, the dosage of the drugs administered should be reduced to the aforementioned effective minimal levels. Thus streptomycin may be given up to 0.5 Gm. per day, and PAS up to 5 Gm. per day. If the complications persist, the offending drug should be stopped for several days or a week. At this time, unless the patient is drug sensitive, the therapy may be restarted with the use of minimal effective doses. How long it will take for a patient to recover from the complications previously listed seems to vary. Influencing factors are: (1) status of kidney function, (2) possible disturbance of hemopoietic system, (3) degree of patient sensitivity, and (4) type and extent of complication. In addition to stopping the drug, it may be necessary to use infusions of glucose, saline, potassium (Caylet[17]), vitamins, and minerals. In the severe, protracted cases, antihistamines can be used to good advantage. Corticotropins are not to be used as antiallergy medications in patients with tuberculosis. While the mechanism is not clear, Ebert[18] has reported to the American Trudeau Society that there was good evidence that tuberculosis had been made worse as a result of the use of hormones (ACTH or cortisone).

Clinical Results

While PAS does not possess as much suppressive effect against the tubercle bacillus as streptomycin, it may be used more generously. If effective, one may note the same beneficial effects outlined in our previous publications.[7, 8] The patient begins to experience an enhanced sense of well-being, temperature begins to level off, appetite improves, postprandial pain subsides, weakness and fatigue decrease, increases in weight become very conspicuous, distention subsides, fluid waves gradually disappear, bowel function improves, accelerated sedimentation rates are lowered, the relative leukopenia and lymphocytosis (unless mixed infection is present) begin to shift toward normal levels, increases in hemoglobin and red blood cells are noted, menstrual dysfunction may correct itself, amenorrheic patients frequently begin to menstruate, purulent leukorrhea begins to clear up as the discharge diminishes, while, in tuberculosis of the cervix, vaginal bleeding gradually subsides.

While these subjective and objective findings are also noted with streptomycin, combined therapy provides for safer and more prolonged periods of therapy. In some forms of fibroplastic types of genital tuberculosis, with or without ascites, the longer the patient can be treated the less likely the need for surgery. The advanced forms of hyperplastic genital tuberculosis, and/or caseous lesions most frequently necessitate surgery. Such patients are now better able to withstand the rigors of operative procedures, lines of cleavage are more readily available, the patient's own recuperative powers are definitely improved, the vaginal vault as well as the abdominal wall can be closed primarily, and there need be no fear of wound dehiscence.

The serious complications of recurrences or relapses have been encountered in but one patient, since the use of combined therapy. In the follow-up clinic such possibilities are constantly kept in mind. In previous reports it was indicated that, with the use of the streptomycin group alone, relapses occasionally did not respond to further therapy. The addition of PAS has lessened that possibility but by no means has it been eliminated.

Of the 18 patients being reported in this series, 5 patients were subjected to surgery with a diagnosis other than genital tuberculosis. In order of frequency the diagnoses were: (a) chronic pelvic inflammatory disease with bilateral adnexal masses; (b) bilateral tubovarian masses; (c) intestinal obstruction; (d) chronic cervicitis and chronic adnexitis, and (e) carcinoma of the cervix. The lesions in two patients were minimal enough so that a total hysterectomy and bilateral salpingo-oophorectomy were done. A full course of streptomycin and PAS was given postoperatively to each (120 days). The other two patients revealed far-advanced lesions warranting only biopsy and immediate closure. Under intensive postoperative PAS and streptomycin therapy (3 months), the response was so favorable that further surgery to this day has not been deemed necessary. Repeated biopsies and cultures have been negative for tuberculosis. The fifth patient was subjected to a modified Wertheim procedure. Biopsies revealed not only carcinoma of the cervix, but tuberculosis of the oviducts as well.

One patient had been operated upon for genital tuberculosis one year prior to her present admission. At the time of surgery she was subjected to a total hysterectomy and bilateral salpingo-oophorectomy, and had received streptomycin pre- and postoperatively. The diagnosis on her second admission was recurrent tuberculous peritonitis. On this occasion she received streptomycin and PAS treatment for 3½ months. Her response was prompt and excellent. To date there has been no further evidence of recurrence.

Six patients had correct diagnoses of genital tuberculosis by the usual methods of history, physical examination, biopsies, cultures, x-rays, etc. These patients responded to combined streptomycin and PAS, so that surgery was not necessary. Repeated cultures and smears have been negative.

Six other patients also had correct preoperative diagnoses of genital tuberculosis. Five received combined streptomycin and PAS for periods varying from 3½ to 4 months preoperatively, and for 3 weeks postoperatively. The advanced, mixed type of pathology which was found at surgery necessitated in each of them a total hysterectomy and a bilateral salpingo-oophorectomy.

The sixth patient represents the only mortality in the series.

Mrs. R. W., a 16-year-old Negro, acutely ill and somewhat emaciated, who had delivered a full-term male fetus 5 months before, entered Cook County Hospital with the following complaints: (a) missed the last 2 menstrual periods, (b) persistent abdominal distress for one month, (c) abdominal swelling for one week, (d) postprandial pain for one week, (e) progressive weight loss for 5 months, and (f) purulent vaginal discharge. Physical examination revealed: a temperature of 101° F., blood pressure 106/68, pulse 120, the abdomen moderately distended with questionable doughiness, and an indefinite mass in the right lower quadrant arising out of the pelvis. Bimanual examination revealed: a parous introitus, a copious amount of mucopurulent discharge, the corpus not adequately outlined, the right adnexa replaced by a large doughy mass extending into the abdomen, only slightly tender, and adherent; the left adnexa were thickened and infiltrated. The clinical impression was tuberculous adnexitis and peritonitis; however, the possibility of an abdominal pregnancy had to be ruled out. The Aschheim-Zondek test was negative. Her red blood count and hemoglobin were 2.86 million and 28 per cent, respectively, and the white blood count was 5,700. For 3 days the temperature spiked to 103° F., despite blood, fluids, and intensive penicillin therapy. A flat plate of abdomen was not noteworthy. On the fourth day streptomycin and PAS were added to her therapy, and the patient began to improve. On the twentieth day she seemed remarkably better but no changes had occurred in the pelvic or abdominal findings. On the thirtieth day she suffered a sudden relapse, initiated by elevations of temperature, followed by chills and fever, and more abdominal pain. It was felt that the patient might have suffered a rupture of a pelvic viscus. The patient failed to rally, and on the thirty-fifth day an exploratory laparotomy was done, with the bone that drainage or extirpation of the adnexa might help. The findings were those of a diffuse adherent hyperplastic type of tuberculosis, with no evidence of a ruptured abscess or viscus. Adequate entry into abdomen or pelvis was impossible. Biopsies were taken and the abdomen was closed. Preoperatively the white blood count was 4,300, the hemoglobin 70 per cent, and the red blood count 3.67 million. The patient died 4 days later. An autopsy was denied by her family. The biopsy reports were positive for tuberculosis.

This case illustrates several important clinical facts. First, it should be noted that pelvic and/or abdominal tuberculosis may appear shortly after delivery. We have seen 3 such cases during our 4 year study of genital tuber-

culosis. Abdominal distention with or without ascites that appears within a few months after delivery must of necessity call to mind the possibility of tuberculosis.

Second, genital tuberculous infections appearing after childbirth seem to be more severe than similar lesions unassociated with pregnancy. This patient had a fulminating type which was resistant to all therapy. Unfortunately, the actual cause of death is obscured by the lack of autopsy findings. From the clinical manifestations, she died of miliary tuberculosis. The other two patients previously mentioned, though not part of this series, responded favorably and are still alive.

Comment

Clinical evidence definitely indicates that streptomycin (dihydro) when used with PAS is superior to treatment with either of these drugs singly. Combined therapy is superior because the development of resistant bacterial strains is inhibited or significantly delayed; both drugs, possessing bacteriostatic and possible bactericidal effects, are able to be tolerated over longer periods of time. The patient's own powers of recovery are increased; and if surgery eventually becomes necessary, the patient is better prepared for it.

The more recent introduction of the isonicotinic acid hydrazines in no way minimizes the value of combined PAS and streptomycin therapy. Bacteriological evidence is accumulating to show that the tubercle bacillus often shows increasing resistance to the hydrazines.[19, 20] It has already been strongly stressed in the literature that "isoniazid be employed in multiple combinations with streptomycin or PAS or other chemo-therapeutic agents active against the tubercle bacillus."[21] Continued intensive study is desirable, and, for that reason, we have already started investigations with the hydrazides in the gynecological department of the County Hospital. In conclusion, we feel that *for the present* although isonicotinic acid hydrazines are of great importance, especially when resistance or sensitivity to streptomycin has developed, combined streptomycin and PAS treatment is the most desirable approach to the medical management of genital tuberculosis.

Summary and Conclusion

1. Eighteen consecutive cases of genital tuberculosis treated with PAS and dihydrostreptomycin are herewith presented.

2. The average dose of streptomycin was 1 Gm. per day given in a single intramuscular injection. The dosage of PAS was 10 Gm. per day. The duration of combined drug therapy was as a rule 3½ to 4 months.

3. The side reactions and toxic behavior of PAS are discussed; and the management of these complications is considered in detail.

4. PAS may be used for its suppressive effects long after the tubercle bacillus has become resistant to streptomycin.

5. Although our objective has been to give both drugs for as long as possible in an effort to avoid surgery, it has been found that advanced forms of genital tuberculosis usually necessitate extirpational procedures.

6. The addition of PAS to our therapeutic armamentarium has lessened the possibility of relapses and recurrences.

7. The clinical-pathological peculiarities of tuberculosis are such that the diagnosis may easily be missed. Thus, 5 of these 18 patients were subjected to initial surgery with a diagnosis other than genital tuberculosis. The other 13 cases were correctly diagnosed and managed accordingly.

8. Abdominal distention with or without ascites, appearing within a few months after abortion or delivery, should strongly suggest the possibility of genital tuberculosis.

9. The advantages of combined antimicrobial therapy are outlined.

10. The recent introduction of the isonicotinic acid hydrazines in no way minimizes the value of combined PAS and streptomycin therapy.

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THE VERATRUM TREATMENT OF TOXEMIA OF PREGNANCY: A CONTROLLED STUDY*†

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ALTHOUGH *Veratrum viride* has been used in the treatment of toxemias of pregnancy for many years, and several recent reports have attested to its value,[1-5] the drug is still not widely used. In an attempt to justify its use and to compare its effectiveness with that of currently accepted methods of therapy the following study was undertaken.

Using the alternate case technique 50 patients with severe pre-eclampsia received purified extracts of *Veratrum viride* given intramuscularly and 50 patients received pentobarbital and magnesium sulfate given intravenously. All patients fulfilled Dieckmann's criteria of blood pressure over 160/110 mm. Hg, more than one plus albuminuria, and more than one plus edema.

During the past year and one-half at this hospital there have been only 12 patients with eclampsia. The results of these cases treated with purified extracts of veratrum given intravenously are compared with the results in the last 12 patients with eclampsia treated at this hospital with intravenous pentobarbital and magnesium sulfate.

Finally, the results in an additional 308 patients with nonconvulsive toxemia treated with purified extracts of veratrum given intramuscularly are analyzed.

Three purified products of *Veratrum viride* were used in this study: Vergitryl (Squibb), Veriloid (Riker) and 1.N 66‡ (Irwin, Neisler). The dosage, hypotensive effect, and incidence of toxicity were similar in all three, with the exception of 1.N 66, which caused less vomiting when given intravenously.

Method of Administration and Dosage

The finding that there was an average effective intramuscular dose of purified veratrum greatly simplified the use of the drug and permitted the adoption of the following treatment schedule for all nonconvulsive toxemias of pregnancy:

1. Give purified veratrum, e.g., 0.5 c.c. Vergitryl (0.75 unit), 0.5 c.c. Veriloid (0.5 mg.), 0.5 c.c. 1.N 66 (1 mg.), mixed with 1 c.c. of 1 per cent procaine intramuscularly at once.

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‡A *Veratrum viride* alkaloid Cryptenamine.

2. Record the blood pressure and pulse every half hour.

3. Repeat purified veratrum, 0.5 c.c. intramuscularly, whenever the blood pressure is over 140/90. Veratrum may be given as often as every hour, if necessary.

4. If there is no hypotensive effect from 0.5 c.c. of purified veratrum at the end of one hour, increase dosage to 0.6 c.c.

5. If nausea or vomiting occurs give 50 mg. pentobarbital sodium intravenously.

Observations of the blood pressure chart and evaluation of the patient will soon inform the physician of the patient's sensitivity to veratrum. For example, one may find that 0.5 c.c. of purified veratrum will maintain the blood pressure under 140/90 from 3 to 6 hours. Veratrum is then repeated at 3 hour or 6 hour intervals as the case demands. The amount and the dosage intervals may vary from patient to patient without correlation with the initial height of the blood pressure or the severity of the toxemia state. The management of each patient, therefore, must be individualized.

This is exemplified by the following case of severe pre-eclampsia.

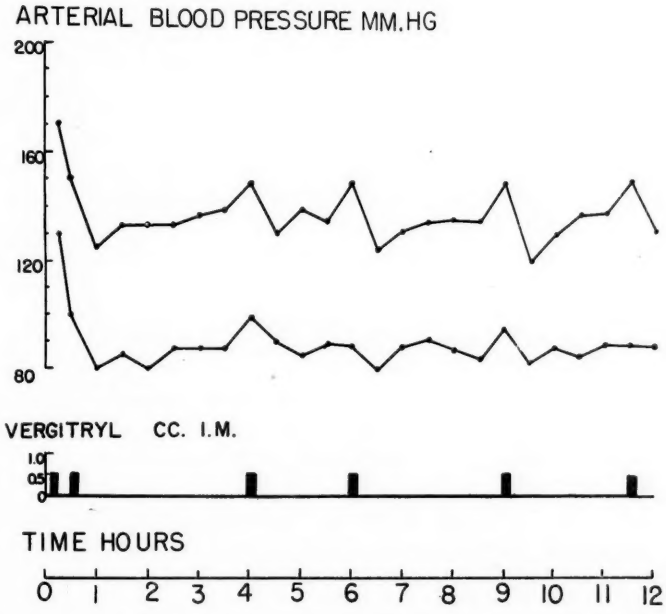

Fig. 1.—Chart of arterial blood pressure of patient G. S. (From Finnerty, F. A., Jr.: New England J. Med. 246: 246, 1952.)

CASE 1.—G. S., a 15-year-old primigravida, was admitted in the seventh month of pregnancy with a history of an uneventful prenatal course until one week before entry, when she noted the development of marked swelling of the ankles and face and moderate occipital headache. Physical examination revealed a blood pressure of 170/130. There was spasm of the retinal arteries. The heart and lungs were normal. Abdominal examination revealed a 7 month intrauterine pregnancy. There was massive edema of the face, hands, and feet. Urinalysis revealed three plus albuminuria. The patient received 14 intramuscular injections of 0.5 c.c. of Vergitryl during the 4 day period prior to delivery (Fig. 1). On the fourth day the fetal membranes were ruptured and she spontaneously delivered a premature living infant who weighed 4 pounds. During the 4 day period following delivery she received fifteen 0.5 c.c. intramuscular doses of Vergitryl, and the blood pressure remained under 140/90.

Comment.—The patient was fully conscious at all times and was able to eat a salt-free diet. No vomiting occurred. The urinary output remained excellent and edema decreased twenty-four hours after the institution of veratrum.

In the true hypertensive patient, with a history of hypertension antedating pregnancy, a reduction in arterial pressure to 140/90 mm. Hg is neither practical nor necessary. In this group of patients a higher level of arterial pressure, e.g., 160/110 mm. Hg is used as an indication for further veratrum.

One further point deserves mention. After a hypotensive response has been obtained with veratrum, e.g., a blood pressure reduction from 160/110 to 130/70 mm. Hg, there is a temptation to repeat the dose at this normotensive level in the hope of keeping the blood pressure in this range. Experience teaches, however, that veratrum repeated at this level of arterial pressure does not prolong the normotensive period, but only causes nausea and vomiting. Veratrum should not be repeated, therefore, until the arterial pressure is at the beginning of the upswing.

Since convulsive toxemia of pregnancy is a medical emergency, the intravenous route for administering veratrum is utilized.

1. Mix 0.5 c.c. of purified veratrum with 20 c.c. of 5 per cent dextrose in water for intravenous use. With one physician recording the blood pressure every minute and another administering the medication, give the veratrum solution intravenously at the rate of 1 c.c. per minute until the first 20 mm. fall in systolic or 10 mm. reduction in diastolic pressure occurs.
2. Leave the needle in the vein. Do not give additional veratrum for there will frequently be a precipitous drop in pressure in the subsequent one to two minutes.
3. If after waiting one to two minutes no such reduction occurs, proceed with veratrum administration at a rate of 1 c.c. per minute, stopping at the first subsequent sign of hypotension.
4. Remove the needle. Replace the needle with a 15 gauge needle through which a sterile polyethylene plastic catheter is threaded well into the vein. Remove the 15 gauge needle and tape the catheter to the skin of the forearm.
5. Begin giving a solution of 5 per cent dextrose in water through the catheter to ensure patency. All additional medication is given through this catheter.

After the first hypotensive effect of veratrum has been witnessed, the catheter being in place, blood pressure recordings are made at 15 minute intervals. Additional veratrum (half the previous effective dose) is given whenever the blood pressure is 140/90 or above. Once again, a few hours of observation of the blood pressure chart and clinical appraisal of the patient will demonstrate the need for veratrum at definite intervals, such as every forty minutes or every 2 hours, the interval between injections becoming longer as the severity of the condition diminishes. If vomiting occurs, 50 mg. of pentobarbital sodium is administered intravenously.

The decision concerning the time and type of delivery is left entirely to the obstetrician. Generally speaking, however, after the blood pressure has been stabilized for 24 to 48 hours, if a viable fetus is present, the most indicated method of delivery is resorted to.

During labor and delivery, if the patient is allowed to deliver per vaginam, and similarly during surgery, if cesarean section is selected as the method of delivery, there is no change in the veratrum regime. The same routine is followed during the first 24 hours postpartum or until the blood pressure has become stable and signs and symptoms of toxemia have disappeared.

The following case illustrates the necessity of careful observation and prompt and intensive treatment with veratrum in an eclampsia patient.

CASE 2.—E. G., a 24-year-old Negro primigravida, was admitted in the thirty-fourth week of pregnancy with a history of dizziness, frontal headache, and edema of the ankles of two weeks' duration, all symptoms having gradually increased in severity. She had had no prenatal care. She had two generalized convulsions on the day of admission and was in a convulsion when seen in the admitting office. The blood pressure was 210/110. Funduscopic examination revealed arteriolar spasm with a retinal sheen. There was edema of the face, hands, and pretibial region. The heart and lungs were within normal limits. Abdominal examination revealed a 34 week intrauterine pregnancy. Examination of the urine revealed four plus albuminuria.

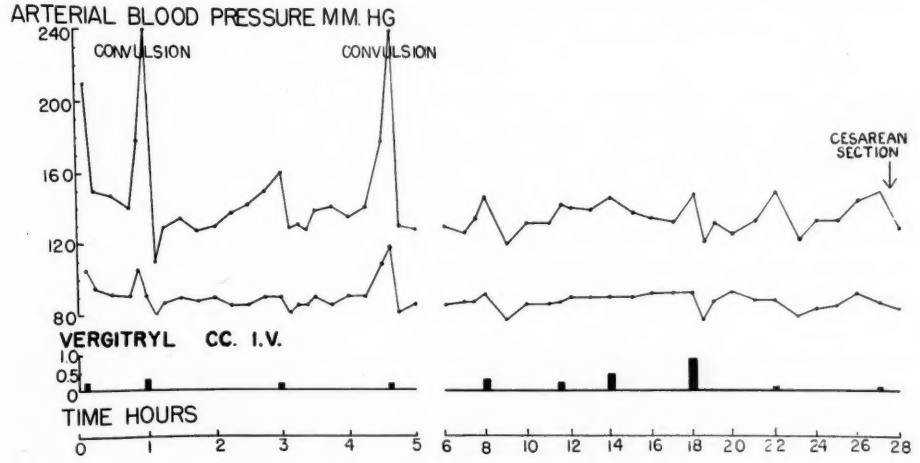

Fig. 2.—Chart of arterial blood pressure of patient E. G. (From Finnerty, F. A., Jr.: New England J. Med. 246: 246, 1952.)

A polyethylene catheter was inserted into the brachial vein and an infusion of a solution of 5 per cent dextrose in water was started. Vergitryl (0.5 c.c. in 20 c.c. of 5 per cent dextrose in water) was given intravenously, and a total dose of 0.3 c.c. produced a fall in blood pressure from 210/105 to 150/95. The effect of this initial dose on the blood pressure lasted 45 minutes (Fig. 2). During preparation of the perineum, the blood pressure was inadvertently allowed to rise to 175/105 and then to 240/90, at which time a convulsion occurred. Vergitryl was immediately administered in a dose of 0.37 c.c.; this produced a prompt fall in pressure to 110/80. The blood pressure remained under 150/100 for 3 hours, during which time one additional intravenous injection of 0.3 c.c. Vergitryl was given. For a period of 25 minutes the blood pressure was not recorded. The blood pressure was then found to be 170/105, which was not treated promptly. Further elevation to 225/110 followed, and the patient had her second convulsion while under therapy. Vergitryl, 0.3 c.c., again caused a prompt reduction in pressure to 120/75. From this point on, blood pressures were recorded promptly at 15 minute intervals, Vergitryl being administered through the polyethylene tubing whenever there was a rise to 140/90. For the remaining 27 hours the patient remained fully conscious, the average blood pressure for this period being approximately 150/100. A total dose of 4.1 units of Vergitryl was given in the 28 hour period. Twenty-four hours after admission, a low-flap cesearean section was performed under ether and gas anesthesia; a living infant that weighed 3 pounds, 9 ounces was delivered. After the operation the blood pressure was recorded at 15 minute intervals for 8 hours, Vergitryl being given intravenously for 8 hours whenever the blood pressure rose over 140/90. Only two 0.3 c.c. injections were needed. The remainder of the course was uneventful.

Comment.—The direct relationship between the elevation of blood pressure and the production of convulsions is seen in Fig. 2. Furthermore, since the patient was fully conscious throughout the toxemic period, she was able to inform the staff of periods of anxiety and increased tension. This subjective tension was soon followed by a rise in arterial pressure and then by a convulsion. For this reason it seemed evident that increased anxiety was the first indication of the need for further treatment. Vergitryl not only lowered the blood pressure but also relieved the feeling of anxiety.

The urinary output was excellent—more than 2,000 c.c. the first 24 hours and more than 3,500 c.c. daily from then on. Edema was less 8 hours after admission, and examination of the retina 6 hours after admission showed a marked reduction in arteriolar spasm. Vomiting occurred on two occasions and was readily controlled by 50 mg. of pentobarbital sodium given intravenously. Finally, the use of the polyethylene catheter not only permitted repeated painless administration of intravenous medication but also did away with the need of restraining the patient.

Duration of Action.—

Veratrum given intramuscularly begins to show its hypotensive effect in 20 minutes and reaches its peak of action in 45 minutes. The duration of hypotension is variable, lasting from 1 hour to 8 hours; the average is 3½ to 4 hours.

An effective intravenous dose of veratrum in the mixture used has its hypotensive effect in one to two minutes. The duration of action is again variable, depending on the individual sensitivity to the drug, the amount of anxiety and tension present, and the severity of the toxemic state.

Toxicity.—

Veratrum given intramuscularly caused pain at the site of injection. This local reaction was greatly minimized by mixing 1 c.c. of 1 per cent procaine in the same syringe with the veratrum. The only systemic toxic manifestations of veratrum were related to the gastrointestinal tract and were probably due to the vagal stimulation produced by the drug. Increased salivation, nausea, vomiting, and diarrhea were seen. The increased salivation frequently preceded vomiting. When seen alone, it was transitory and was seldom objectionable.

Nausea and vomiting were seen in 43 of the 370 cases (358 cases of nonconvulsive toxemia and 12 of convulsive toxemia). These toxic manifestations were most common after intravenous administration of veratrum, occurring in 9 of the 12 patients with eclampsia.

After intravenous administration of veratrum the vomiting usually preceded the hypotension by a few minutes, but was frequently associated with the fall in pressure and lasted for 5 to 10 minutes. Successive doses produced less vomiting. Vomiting, though alarming if not expected, was never so severe as to require parenterally given fluids. Further, since all these patients were conscious, aspiration was never a problem. Of the three purified products of veratrum used, 1.N 66 caused less vomiting when given intravenously.

When vomiting resulted from intramuscular administration of veratrum it occurred 15 to 20 minutes after injection, thus preceding the peak hypotensive effect by one-half hour.

Of the many drugs used to combat vomiting, small intravenous doses of a barbiturate were found to be most effective. In this series 50 mg. of pentobarbital sodium was given whenever vomiting occurred. Recent evidence strongly suggests that the addition of procaine to purified veratrum for intramuscular injection definitely diminishes the incidence of vomiting.[8] Finally, since vomiting is more frequent if the stomach is full, an attempt was made to regulate the schedule so that veratrum was not given less than one hour before or two hours after a meal.

Though tolerance seldom occurred during the first 4 days of therapy it was not an uncommon occurrence after 5 or 6 days. Not only were larger doses of veratrum needed to maintain the hypotensive effect but the interval between doses became shorter. A higher than average incidence of vomiting was seen here. It was for this reason, then, that, after the blood pressure had been stabilized for 24 to 48 hours, if a viable fetus was present, induction of labor was advised.

There have been 6 instances of tachyphylaxis (a temporary refractory period) during veratrum therapy, 4 following intravenous administration and 2 following intramuscular administration. This phenomenon was characterized by a temporary rise in arterial blood pressure, frequently to above pre-treatment levels, and a definite bradycardia, e.g., pulse under 70. During this period, repeated injections of veratrum exerted no hypotensive effect. When medication was withheld for 3 to 4 hours, the patient again responded to the usual doses of the drug. Since termination of this refractory period could readily be detected by an increase in pulse rate, veratrum was promptly reinstituted when the pulse rate exceeded 70 beats per minute. The bradycardia characteristic of this phenomenon seemed to protect the patient from vascular and cerebral complications for no untoward complications were witnessed during tachyphylaxis.

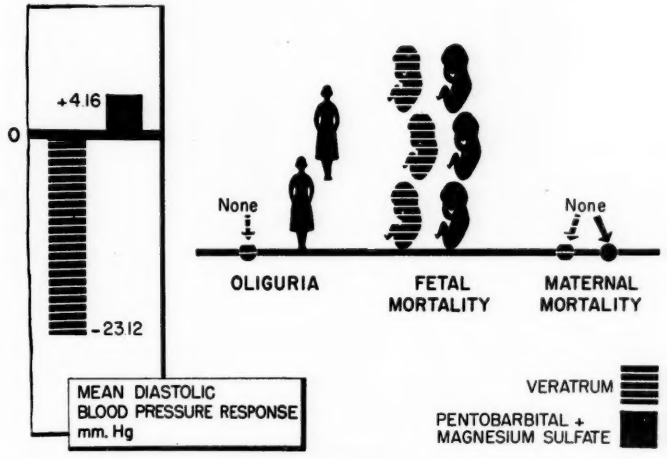

Fig. 3.—The results of therapy in 100 cases of severe pre-eclampsia.

Results

Control Study.—

The veratrum group of patients with severe pre-eclampsia were treated with intramuscular veratrum as outlined above. The control group of patients received pentobarbital and magnesium sulfate intravenously in doses ranging between 250 mg. pentobarbital plus 5 Gm. of magnesium sulfate in 5 hours to 2,800 mg. pentobarbital and 27.5 Gm. of magnesium sulfate in 48 hours. The average dose was 1,200 mg. pentobarbital plus 15 Gm. magnesium sulfate intravenously in 12 hours.

The results of the therapy in the 100 cases of severe pre-eclampsia are depicted in Fig. 3. The striking contrast in mean diastolic blood pressure response is clearly seen with a fall of 23.12 mm. Hg in the veratrum group and an actual increase of 4.16 mm. Hg in the pentobarbital group. Albuminuria

persisted 48 hours after therapy was instituted in 9 of the pentobarbital group and in one of the veratrum-treated cases. Oliguria was seen in 2 of the pentobarbital group and in none of the veratrum group. There were 3 fetal mortalities in each group. No maternal mortalities occurred in either group.

The only complication in the veratrum group were 9 cases of vomiting. Complications in the control group included 4 cases of coma and one cerebrovascular accident.

The results of the 12 cases of eclampsia treated with purified extracts of veratrum given intravenously are contrasted with the results of the last 12 cases of eclampsia treated at this hospital with intravenous pentobarbital and magnesium sulfate in Figs. 4 and 5.

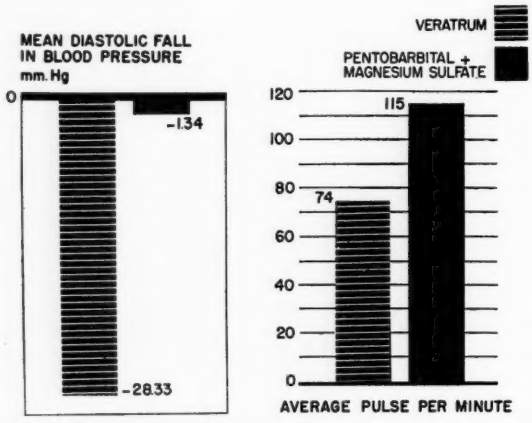

Fig. 4.—Response of diastolic blood pressure and pulse rate to therapy in 24 cases of eclampsia.

The veratrum cases were treated with intravenous veratrum as outlined above. The control group received pentobarbital and magnesium sulfate intravenously in the same dosages as described for the pre-eclampsia cases. Induction of labor or cesarean section was employed in both groups of patients 24 and 48 hours after institution of therapy. The types of delivery were similar in both groups (Table I).

TABLE I. TYPES OF DELIVERY IN THE 24 CASES OF ECLAMPSIA

VERATRUM		PENTOBARBITAL AND MAGNESIUM SULFATE	
Cesarean	6	Cesarean	5
Forceps	4	Forceps	5
Spontaneous	1	Spontaneous	1
Version and extraction	1	Not delivered	1

Again, the lack of diastolic blood pressure response with pentobarbital is striking with an average fall of 28.33 mm. Hg in the veratrum group and a 1.34 mm. Hg reduction in the pentobarbital group. The veratrum-treated cases manifested either a normal pulse rate or bradycardia; the pentobarbital group consistently showed a tachycardia.

Convulsions after institution of therapy occurred in 6 of the veratrum cases and in 9 of the pentobarbital-treated cases. Fifty per cent (6 cases) in the pentobarbital group manifested oliguria; no cases of oliguria were seen

in the veratrum group. Twenty-five per cent (3 cases) of the pentobarbital group were complicated by anuria (lower nephron nephrosis); anuria was not seen in the veratrum-treated cases. There were 2 fetal deaths in the veratrum group, 4 in the pentobarbital group. There was 1 maternal death in the pentobarbital group, none in the veratrum group.

Toxicity of the Drug: Ten of the 12 veratrum cases manifested mild vomiting. In the pentobarbital group, there were 2 instances of atelectasis and one instance of aspiration, ultimately causing death (Table II).

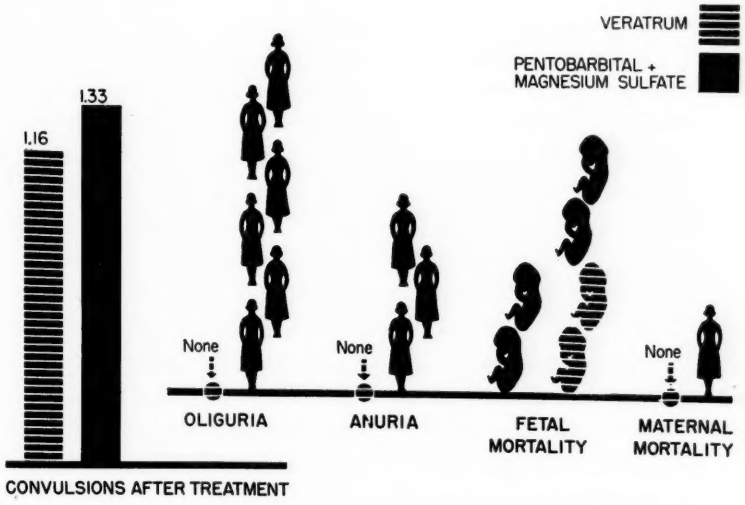

Fig. 5.—The results of therapy in 24 cases of eclampsia.

Complications: After cessation of veratrum therapy, one patient developed a supraventricular tachycardia, which was controlled by digitalis. In the pentobarbital group there were 2 instances of postpartum psychosis, one cerebrovascular accident, and one maternal death (Table II).

TABLE II. TOXICITY OF THE DRUGS USED AND COMPLICATIONS SEEN IN 24 CASES OF ECLAMPSIA

TOXICITY OF DRUG		COMPLICATIONS	
Veratrum.—			
Vomiting	10 cases	Supraventricular tachycardia	1 case
Pentobarbital and Magnesium Sulfate.—			
Atelectasis	2 cases	Postpartum psychosis	2 cases
Aspiration	1 case	Cerebral vascular accident	1 case
		Maternal death	1 case

Uncontrolled Study.—

The results of therapy in the additional 308 patients with nonconvulsive toxemia treated with veratrum given intramuscularly are analyzed in Table III.

Patients with blood pressures over 150/100, edema of the face and ankles, albuminuria—particularly if they were below the age of 20—were considered

to have severe pre-eclampsia. In the 30 cases of severe pre-eclampsia there were 22 excellent results, 6 good results, 1 fair result, and 1 poor result.

An excellent response was defined as a good hypotensive response, disappearance of symptoms, decrease of edema, and no toxicity. A good result was defined as a satisfactory hypotensive response, disappearance of symptoms and decrease of edema, with mild nausea and vomiting. A fair response consisted of a modern hypotensive response and decreasing symptoms and signs of toxemia with moderate vomiting. A poor response was defined as no hypotensive response or the presence of a hypotensive response with severe vomiting.

TABLE III. RESULTS OF TREATMENT WITH PURIFIED EXTRACTS OF VERATRUM IN NONCONVULSIVE TOXEMIAS

TYPE OF TOXEMIA	NO. OF CASES	RESULTS			
		EX-CELLENT	GOOD	FAIR	POOR
Severe pre-eclampsia	30	22	6	1	1
Mild pre-eclampsia	150	126	18	3	3
Hypertensive vascular disease	17	6	10	0	1
Hypertension and superimposed toxemia	30	17	8	4	1
Postpartum toxemia	81	70	8	3	0
Total	308	241	50	11	6
Per cent		78	17	3	2

Patients with blood pressures over 140/90, with or without albuminuria, and with or without edema, who had no hypertensive vascular changes in the retinas, were given the diagnosis of mild pre-eclampsia. In the 150 cases, there were 126 excellent results, 18 good results, 3 fair results, and 3 poor results.

Patients who were admitted with histories of hypertension antedating pregnancy and who showed elevated arterial pressure, hypertensive retinopathy, with no edema or albuminuria, received diagnoses of hypertensive vascular disease. The results in the 17 cases studied show an excellent response in 6 cases, a good response in 10, and a poor response in one.

Patients who were admitted with histories of hypertension antedating pregnancy and who showed elevated arterial pressure, hypertensive and vasospastic vascular changes in the retinas, and peripheral edema and albuminuria without congestive heart failure, were considered to have hypertensive vascular disease with superimposed toxemia. In the 30 cases studied there were 17 excellent results, 8 good results, 4 fair results, and 1 poor result.

Postpartum pre-eclampsia was diagnosed in patients who had a normal pregnancy with no signs or symptoms of toxemia, but after delivery had an elevated blood pressure above 140/90. In the 81 cases studied there were 70 excellent results, 8 good results, 3 fair results, and no poor results.

There were 5 fetal deaths (1 per cent), and no maternal deaths.

Comment

Veratrum is by no means the final answer or the specific treatment for toxemias of pregnancy. Neither is parenterally given veratrum effective nor

is it practical for long-term therapy, for tolerance not uncommonly develops after 5 or 6 days. Furthermore, we cannot justly attribute the over-all good response in our veratrum-treated cases solely to the drug, for in most cases early induction of labor or cesarean section was employed. The data presented, however, demonstrate that veratrum (1) simplified the management of toxemias, (2) controlled the diastolic blood pressure and pulse rate, and (3) maintained consciousness, thus better preparing these patients for early induction of labor or surgery.

No claim of simplicity can be attached to veratrum given intravenously in the treatment of the convulsive toxemias. Constant observation of the patient, frequent blood pressure recordings, and prompt and intensive treatment when elevations in arterial pressure above 140/90 mm. Hg occur are mandatory. However, the availability of purified veratrum and its effectiveness by the intramuscular route in standard dosage has greatly simplified the management of the nonconvulsive toxemias.

The ability of veratrum to lower blood pressure has never been doubted. Indeed, the main objection to the use of crude extracts of the drug was the danger of causing profound hypotension with resultant oliguria or anuria.[6, 7] Purified veratrum administered as described herein seldom produced a drastic fall in blood pressure to collapse levels thus explaining the lack of oliguria in our cases. The effect of veratrum on the diastolic pressure is clearly seen in Figs. 3 and 4 with an average fall of 23 mm. Hg in the cases of severe preeclampsia and a fall of 28 mm. Hg in the eclampsia cases. Though pentobarbital frequently produced a reduction in systolic pressure, the diastolic pressure was seldom altered.

A constant finding in severe toxemias, particularly eclampsia, is tachycardia. Dieckmann[9] states that an increase in pulse rate over 100 should be regarded as indicating increasing severity and further states that the mortality in eclamptic patients with pulse rates over 120 is over 39 per cent. Pentobarbital and magnesium sulfate have no bradycrotic action. Veratrum by its vagal stimulatory action causes a bradycardia (Fig. 4). It is evident then that, following an effective dose of veratrum, the arterial pressure is lower and the pulse rate is slower.

The main difference in our veratrum-treated eclampsia patients and the pentobarbital-treated cases was that the former were conscious, the latter unconscious. Eleven of the 12 pentobarbital-treated patients with eclampsia were in coma for more than 12 hours. No veratrum-treated patient remained unconscious more than 2 hours after institution of therapy. The recent experimental studies of McCall and Taylor[10] on cerebral blood flow and oxygen metabolism in toxemia of pregnancy are in accord with our clinical observation. They found that barbiturates depress cerebral blood flow and are likely to prolong the coma of eclampsia. That persistence of coma in an eclamptic patient is a very grave sign is evidenced by a mortality rate from 34 to 73 per cent in these patients.[9]

Heavy sedation, besides adding to the complexity of management of a seriously ill patient, greatly increases the incidence of respiratory complica-

tions. In the pre-eclamptic patients treated with pentobarbital there were 4 instances of atelectasis and in the 12 pentobarbital-treated eclamptic patients there were 2 instances of atelectasis and 1 instance of aspiration ultimately causing death of the patient (Fig. 5).

It is important to have the full cooperation of the severely toxic patient in order to maintain adequate intake of fluid and nourishment. Veratrum therapy not only allows the patient to take nourishment by mouth, thus better preparing her for delivery or surgery or both, but also permits her to keep the physician informed of any untoward symptoms. Furthermore, hypertensive toxemias are frequently seen in the seventh or eighth month of pregnancy which are crucial months in the development of the fetus. The large doses of sedation routinely employed in the management of severe toxemias have a deleterious effect on the premature infant.

Summary

A simplified and safe method of management of hypertensive toxemias of pregnancy using purified extracts of veratrum viride is outlined.

In 308 cases of nonconvulsive toxemias, intramuscular administration of purified veratrum gave excellent results in 241 (78 per cent), good results in 50 (17 per cent), fair results in 11 (3 per cent), and poor results in 6 (2 per cent). There were no maternal deaths and 5 fetal deaths. Vomiting was the only toxic manifestation which occurred in 34 cases (9 per cent).

In 100 cases of severe pre-eclampsia (Dieckmann's Classification), alternate patients received purified extracts of veratrum viride intramuscularly, and the others received pentobarbital and magnesium sulfate intravenously. In the veratrum group, the average diastolic blood pressure decreased 23.12 mm. Hg. Complications included vomiting (9 cases) and fetal death (3 cases). In the pentobarbital group, the average diastolic pressure increased 4.16 mm. Hg. Complications were oliguria (2 cases), coma (4 cases), cerebrovascular accident (1 case), fetal death (3 cases).

Twelve cases of eclampsia treated with intravenous veratrum were compared with 12 cases treated with pentobarbital and magnesium sulfate. In the veratrum group, the average diastolic pressure decreased 28.33 mm. Hg. Convulsions occurred in 7 instances after treatment was started. Complications were vomiting (10 cases) and fetal death (2 cases). In the pentobarbital group, the average diastolic decreased 3.33 mm. Hg. Convulsions occurred in 9 cases after treatment was started. Complications were oliguria (6 cases), anuria (3 cases), postpartum psychosis (2 cases), atelectasis (2 cases), cerebrovascular accident (1 case), fetal death (4 cases), and maternal death (1 case).

Conclusion

Our data in comparable cases at the same institution suggest that veratrum therapy, because it controls the diastolic blood pressure and pulse rate and maintains consciousness, is a more effective method of management of toxemia of pregnancy than the pentobarbital and magnesium sulfate regime.

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ACUTE INTRAVASCULAR HEMOLYSIS, LOWER NEPHRON NEPHROSIS, AND ACUTE ANTERIOR PITUITARY NECROSIS COMPLICATING A CASE OF SEVERE PRE-ECLAMPSIA

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THE clinical and pathological features of lower nephron nephrosis have been very ably described at length by Bywaters,[1] Lucke,[2] and several other investigators,[3-6] and need not be repetitiously related here. Also, it has been fairly widely accepted that severe hemorrhagic accidents are prone to complicate severe late pregnancy toxemia[7] and thereby contribute to the production of the renal shutdown that ultimately leads to acute renal insufficiency.[2, 9] Sheehan[6] warns that 6 per cent of such cases will develop irreversible severe bilateral cortical necrosis and die in the puerperium if they manage to survive the initial hemorrhagic insult. The "renal shutdown" has been the subject of intense study by several investigators both here in the United States and abroad.[8] Sophian,[9] in his defense of the Trueta shunt theory, indicts concealed intrauterine hemorrhage in the gravid uterus as the initiating factor. He feels that any compression or distention of the pregnant uterus will cause a reflex spasm of the efferent glomerular arterioles, thereby increasing glomerular filtration pressure. A renal pressor substance is formed which prolongs the cortical ischemia and produces tubular damage due to anoxia. The liver cells are likewise affected and focal necrosis of the central or mid-zonal variety results. The sustained constriction of the efferent glomerular arterioles effectively prevents adequate blood flow through the glomeruli and the majority of the circulation is shunted through the juxtamedullary lake apparently producing the so-called afferent glomerular arteriolar spasm. This results in a fall in filtration pressure and prevents the nephron from performing its function of selective absorption and excretion and anuria supervenes. Certain other highly specialized organs are also adversely affected by a sustained period of anoxia.[10] During the latter months of pregnancy the anterior lobe of the pituitary gland is normally hypertrophied and requires a much greater blood supply than in the nonpregnant state. Any sustained period of shock

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from hemorrhage will produce varying degrees of necrosis in the lobe and result in the symptom complex known as Sheehan's syndrome.[10] The severity of such damage is thought to be directly proportional to the duration of anoxia and can only be successfully treated at the time of the accident by immediate, adequate blood transfusions and oxygen. If a peripheral vascular collapse has already occurred, only prompt intra-arterial transfusion will prevent a fatality.[9]

The case to be reported in detail was initially a severe pre-eclamptic toxemia under treatment in our hospital on two separate admissions. Conservative management plus the use of cation exchange resins as outlined in current publications[13, 14] was utilized in treatment. Following an apparently adequate response to therapy the patient developed an acute intravascular hemolytic crisis about 24 hours after an essentially uncomplicated delivery of a normal living infant and plunged precipitately into a state of shock. The acute hemolytic anemia was promptly and adequately treated by immediate blood replacement. A suspected hypokalemic state was corrected by adequate oral ingestion of a commercially available potassium salt and the patient responded satisfactorily. However, during the first twelve hours after the period of shock only negligible quantities of grossly bloody urine were excreted, and it was realized that a renal shutdown had developed despite the prompt blood replacement and other antishock measures utilized. The treatment of the condition was strictly conservative as recommended by Strauss[11] and as fully described in a previous publication of the senior author.[12] The patient appeared to be well oriented throughout her illness and high hopes were held by the attending staff for her eventual recovery. However, despite excellent fluid and electrolyte balance being maintained with the help of flame photometer estimations of serum sodium and potassium, the patient died on the eleventh hospital day, the seventh day of her illness.

S. T. R., a 21-year-old white woman, gravida i, para i, was first seen in the prenatal clinic, U. S. Naval Hospital, Camp Lejeune, N. C., on May 27, 1952, as a transfer from another hospital. The photostatic records she brought with her revealed an essentially uneventful early prenatal course and normal laboratory work. Her last menstrual period was Nov. 28, 1951, and her expected date of confinement was Sept. 2, 1952.

Her first visit at this prenatal clinic was essentially uneventful in that the total weight gain for the pregnancy to date had been 5½ pounds. She had no ankle edema or albuminuria and the blood pressure was within normal limits. On a subsequent clinic visit one month later on June 27, 1952, she had gained 4 pounds and the blood pressure had risen from 116/90 to 128/80. She again had no ankle edema or albuminuria. At this visit she was placed on a 1,030 calorie diet (the standard weight-control diet at this clinic) and advised to restrict salt to a minimum. On the next clinic visit the weight and blood pressure were the same and, although the urine was free of albumin, there was a trace of ankle edema. The patient was placed on ammonium chloride (2 Gm. four times a day for three days) and a return appointment was made for two weeks. At this subsequent clinic visit (on Aug. 8, 1952) her weight had risen from 144½ to 151½ pounds, making the net weight gain 16½ pounds. She had 4 plus pretibial edema, 200 mg. quantitative albuminuria, and the blood pressure was 170/100. It was recognized that this patient had developed a severe pre-eclampsia and was a good candidate for the use of the cation exchange resins. Accordingly, she was admitted to the Dependents' Service, U. S. Naval Hospital, Camp Lejeune, N. C., for treatment.

Following admission to the hospital the patient was placed on 72 Gm. daily of Carbo-Resin* (a preparation containing 12 per cent anion exchange resins; 29 per cent potassium salt of carboxylic acid resin; and 59 per cent carboxylic acid resin) and a regular low-salt hospital diet (containing about 3 Gm. of salt per day) and was allowed bathroom privileges. In addition, she was placed on conservative toxemia management which included morphine sulfate, ⅙ grain every four hours if the blood pressure was above 140/90 and the respirations were not below ten per minute; 2 c.c. 50 per cent magnesium sulfate intramuscularly every four hours as an alternate for morphine; and 2½ grains of Luminal Sodium were given intramuscularly every six hours. Within three days the systolic blood pressure had fallen to less than 140 mm. Hg although the diastolic remained in the neighborhood of 90 mm. Hg. The edema rapidly subsided and the patient felt much improved. The albuminuria fell from 750 mg. per cent to less than 100 mg. per cent. The patient was discharged on Aug. 15, 1952, on the seventh hospital day with a total weight loss of 14 pounds and on 72 Gm. of Carbo-Resin per day. Fig. 1 gives all essential clinical and laboratory data during the first period of hospitalization.

She had tolerated the resin fairly well and no clinical signs of electrolyte imbalance were demonstrable although there were electrocardiographic changes suggestive of very early hypokalemia.

The patient was readmitted to the hospital on Aug. 17, 1952, with the complaint of nausea following the ingestion of the resin. Because of reaccumulation of weight, she was continued on resin therapy (72 Gm. per day). The resin dosages from August 16 through August 19 are only approximations as the patient failed at any time to retain the whole amount. She was also started on Potassium Triplex orally (a preparation containing 15 mg. of potassium per dram), 125 mg. per day. An admission blood count revealed the red blood count to be 3.61 million and the hemoglobin 10 Gm. On the second hospital day the resin dose for the evening was discontinued because of electrocardiographic evidence suggestive of hypokalemia and the oral potassium dosage was increased to 200 mg. daily. An electrocardiogram on the morning of the third hospital day revealed that the hypokalemia was partially corrected and a repeat electrocardiogram late in the afternoon of the same day revealed a further return to normal. The potassium administration was continued throughout the day.

At 12:25 A.M. on August 21, the fourth hospital day, the patient went into spontaneous labor and delivered a 5 pound, 15½ ounce viable female infant under pudendal block anesthesia with outlet forceps. The delivery and immediate postpartum periods were unremarkable. The patient was placed on postpartum toxemia management because of blood pressure elevated to 140/90 and was sent to the recovery room. An electrocardiogram early on the morning of the day of delivery revealed minimal signs suggestive of electrolyte imbalance. The hemogram at this time revealed 3.61 million red blood cells, 11.5 Gm. hemoglobin, and a hematocrit of 37 volumes per cent.

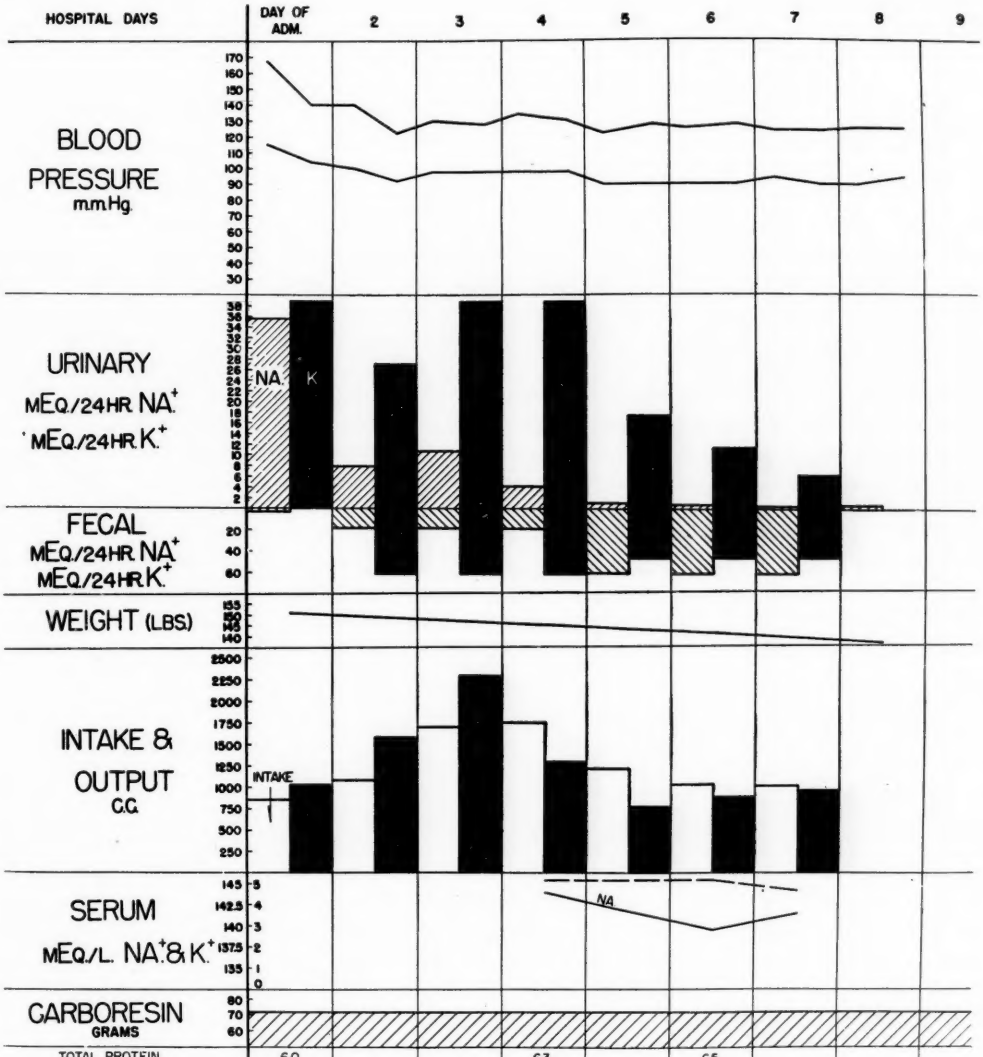
For the first 24 hours the postpartum course was uneventful. Then suddenly at 2 A.M. on the fifth hospital day the patient became cold and clammy and went into shock. Hypokalemia was considered and, accordingly, she was given hourly doses of 60 mg. of potassium orally. She soon "responded" and the blood pressure rose above shock levels.

The patient was re-evaluated at 8:00 A.M. of the same day at which time an electrocardiogram showed no evidence of electrolyte imbalance, but the hemogram revealed an acute anemia. The blood serum was noted to be a deep cherry red and contained hematin crystals in quantity. Jaundice was perceptible and a tender liver edge could be palpated two finger-breadths below the right costal margin. The small quantity of urine excreted was a deep port-wine color.

At this time it was realized that the patient had suffered an acute exacerbation of her toxemia with a complicating extensive intravascular hemolysis producing severe hemoglobinemia. Blood replacement was begun at once. She was placed in an oxygen tent, given penicillin (600,000 units four times a day), cortisone 100 mg. immediately, repeated in six

*The Carbo-Resin and Potassium Triplex used in the treatment of this case were made available without cost by Eli Lilly & Company, Indianapolis, Ind.

hours, then every 12 hours, in an effort to prevent further hemolysis, and afford supportive treatment for shock. The urinary output for the preceding twelve hours had been less than 60 c.c. and resembled pure blood. Although severe lower nephron nephrosis was impending, the patient was transfused with 1,500 c.c. of whole blood that day to combat the severe hemolytic anemia. Early in the afternoon the hemogram had returned to near normal although the blood pressure remained low. The fluid intake for the fifth hospital day was 450 c.c. 5 per cent dextrose in water with vitamins added and 1,500 c.c. whole blood, making a total of 1,950 c.c.



TOTAL PROTEIN	6.0			6.3		6.5		
A/G RATIO	3.6/2.4			3.9/2.4		3.6/2.9		
RBC	3.61			3.60		3.60		
HGB/HCT	10.5/35			10.5/35		10.5/35		
NPN	33.5			29.5		42		
CO_2 cp MEQ/L	32.3			28		42		
BLOOD CHLORIDES MEQ/L	120			120		110		
QUANTITATIVE ALBUMINURIA Mg.%	200	750	100	100	100	120	100	100

Fig. 1.

Following the blood transfusions, an infusion of about 600 c.c. of 5 per cent dextrose in water was then given slowly to which had been added 1.0 c.c. of Levophed.* This was administered at a rate necessary to keep the blood pressure above shock levels. In spite of the Levophed, the blood pressure remained at low normals until the next morning and from that time on remained within normal limits until the death of the patient.

On the morning of the sixth hospital day the hemogram reflected the need for more blood and it was noted the blood serum remained cherry red in color. The patient received 500 c.c. of whole blood and 500 c.c. of 10 per cent dextrose in water with vitamins added. The urinary output was under 60 c.c. and it was concluded that the patient had developed severe lower nephron nephrosis. All subsequent fluids were to be limited to the insensible loss for each 24 hour period (700 to 1,000 c.c.) plus the total urinary output. An electrocardiogram showed no evidence suggestive of electrolyte imbalance and, except for a slight tachycardia, was normal. The red cell count rose from 2.31 million to 3.03 million after the transfusion. The nonprotein nitrogen and uric acid were steadily rising although the blood chlorides and the carbon dioxide combining power were within the normal range. The jaundice did not appear to be deepening and the liver edge had not descended further. The blood pressure tended to remain in the normal range. The urinary output for the sixth hospital day was again 60 c.c. of frankly bloody urine which had a 4 plus reaction to the benzidine test. The seventh hospital day was fairly uneventful. Another 500 c.c. of whole blood and 1,000 c.c. 10 per cent dextrose in water made up the total intake while the urinary output was still about 60 c.c. The blood pressure remained stable and the blood serum was still colored cherry red.

On the eighth hospital day the hemogram again revealed an anemia which was corrected with 500 c.c. whole blood. The rest of the fluid therapy for that day included 350 c.c. of 5 per cent dextrose in water with added vitamins, 400 c.c. 25 per cent dextrose in water, and 30 c.c. 10 per cent dextrose in water, totaling 145 Gm. of glucose in 780 c.c. of fluids. The nonprotein nitrogen and uric acid values were still rising and the blood chlorides had fallen to 85 meq. while the carbon dioxide combining power remained normal. An electrocardiogram taken in the morning showed some minimal damage to the myocardium but no evidence suggestive of electrolyte imbalance. The patient seemed to be somewhat improved and the jaundice appeared to be stationary. The liver had not enlarged. Prostigmine injections and several enemas utilized throughout the hospital stay generally produced adequate relief from abdominal distention. The analysis of the blood on the flame photometer revealed that the potassium was within normal limits and the sodium was moderately depleted. The prothrombin time was elevated (29 seconds with a control of 13 seconds) and intravenous vitamin K was administered. The serum bilirubin and both the direct and indirect van den Bergh reactions were elevated but not to the levels anticipated in comparison to the severity of hemolytic anemia present. It was thought that the patient should continue to receive at least 100 Gm. of glucose intravenously daily in order to protect the liver and effectively decelerate protein catabolism in addition to giving intravenous vitamins. The patient was alert and could spend some time out of the oxygen tent without respiratory difficulty. Flame photometer analyses of the afternoon blood showed a slight rise in the sodium and a significant rise in the potassium of 0.34 meq. At this time it was decided that the serum potassium levels would have to be monitored very carefully and if the value rose above 7.5 meq. Carbo-Resin should be administered either rectally or by stomach tube.[13, 14]

On the ninth hospital day the patient was given 500 c.c. of 10 per cent dextrose in water; 375 c.c. dextrose in water with 120 Gm. of glucose added; and 180 c.c. of oral fluids making a total of 1,055 c.c. The laboratory work revealed the nonprotein nitrogen to be steadily rising, a stationary uric acid level and a carbon dioxide combining power of 46.8 per cent. The red blood cell value was 3.13 million in the morning and 3.92 million in the afternoon. The hematocrit and hemoglobin values were normal. The blood chlorides were 86 meq. and the total urinary chlorides for the previous 24 hour period was 0.33 Gm. The flame photometer level for sodium was 119 meq. and potassium was 4.42 meq. An electrocardiogram taken in the morning revealed equivocal changes suggestive of a very early hyperkalemia. The total protein levels were normal and the prothrombin time

*Levophed is l-norepinephrine (Winthrop-Stearns).

indicated a satisfactory response to vitamin K therapy (prothrombin time of 17 seconds with a control of 12 seconds). The bleeding time was 5 minutes and the clotting time was 3 minutes, 3 seconds. The patient was still well oriented and the liver had not materially enlarged in size since the fifth hospital day. The afternoon blood sample analyzed on the flame photometer was 125.9 meq. for sodium and an increase in potassium to 5.05 meq.

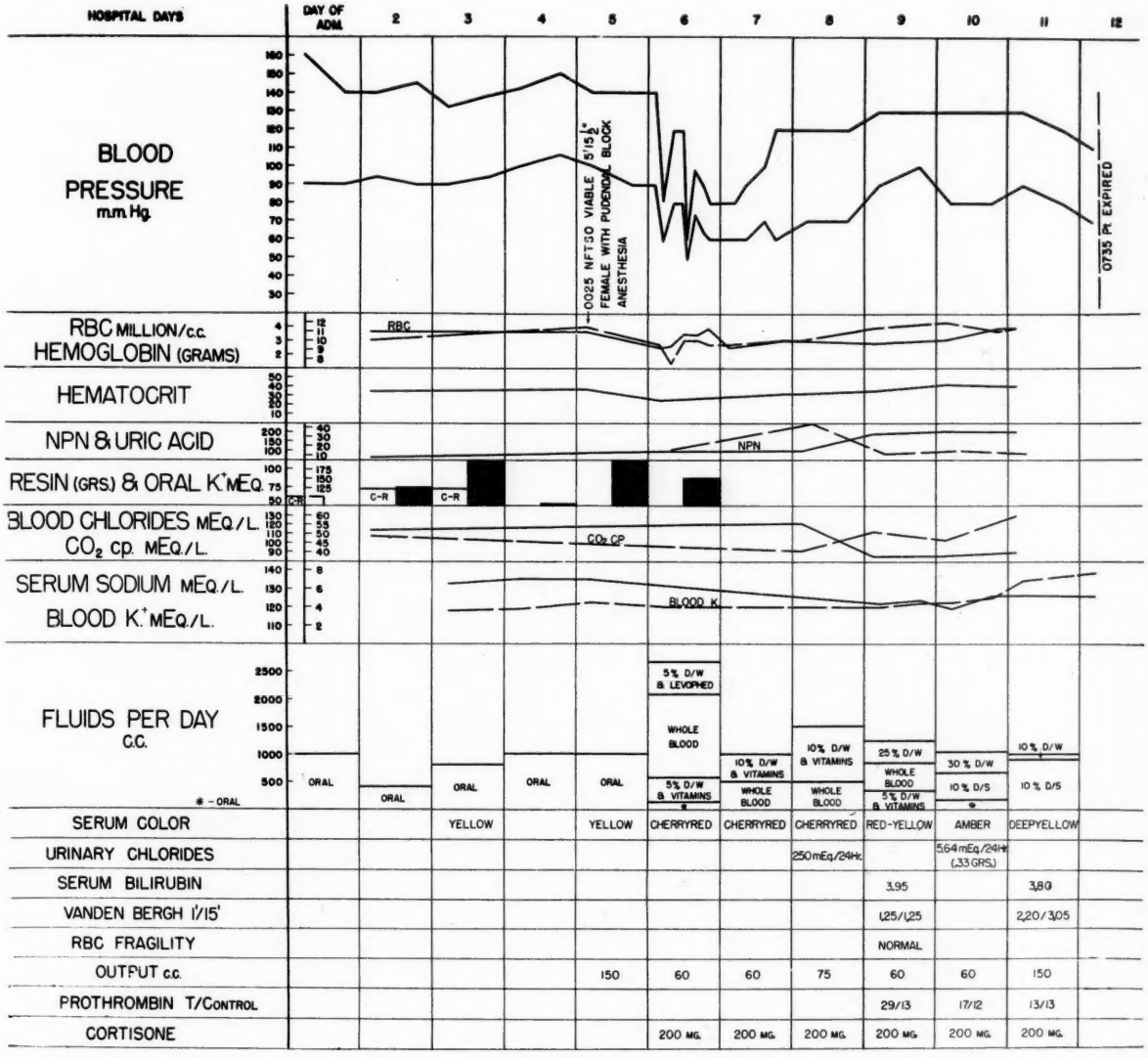


Fig. 2.

On the tenth hospital day the patient began to excrete a yellow-colored urine totaling about 150 c.c. The laboratory work revealed a normal hemogram and despite the nonprotein nitrogen remaining high and the chlorides low (89 meq.) the patient was not seriously out of electrolyte balance. The blood potassium level had risen to 6.82 meq. and it was felt that the time was approaching when the resin therapy would have to be instituted. The prothrombin time was normal and the serum bilirubin had decreased. The patient was given 900 c.c. 10 per cent dextrose in saline to restore the chlorides and 100 c.c. 10 per cent dextrose in water, totaling 1,000 c.c. The patient seemed to be stationary in her

postpartum condition. The lung fields were clear to percussion and auscultation. There was no sacral nor pretibial edema and her respiratory excursions were neither limited nor embarrassed.

The eleventh hospital day was not remarkable until about 7:15 A.M. when the patient began to have respiratory difficulty. Her cardiac action was weak and, in spite of emergency supportive treatment (caffeine, Coramine, etc.), she died at 7:35 A.M. on Aug. 28, 1952.

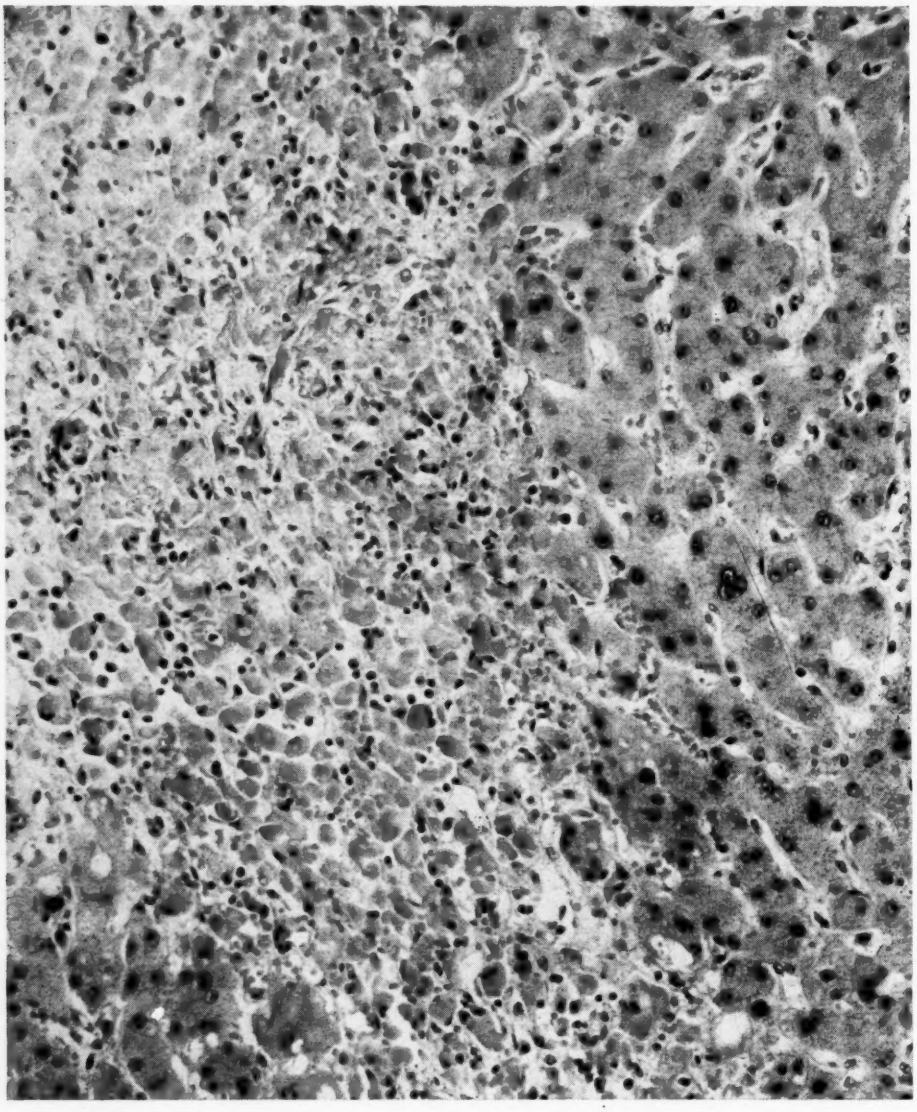


Fig. 3.—Microscopic section of liver exhibiting periportal necrosis with hemorrhagic destruction of tissue. (Armed Forces Institute of Pathology, Picture No. 53 10482.) (×250. Reduced one-third.)

An intracardiac puncture was done one-half hour after death and the blood sample obtained was analyzed on the flame photometer. The values obtained were 125.8 meq. sodium and 7.72 meq. for potassium. No resin therapy had been reinstituted prior to death. Fig. 2 will reveal a complete summary of the laboratory and clinical data during the period of the second hospitalization.

Pathology Report.—

Liver: The liver weighed 2,800 grams, had a yellow tint, and exhibited several areas of irregular, reddish brown hemorrhage and necrosis on the right superior dome. Cross sections showed that these areas extended into the liver parenchyma in well-demarcated patches. Microscopic sections revealed many large infarcts with coagulation necrosis near the periphery associated with a mild, generalized fatty degeneration of the parenchymal cells. In the periportal areas there was a focal necrosis with hemorrhagic destruction of tissue. Many hyaline thrombi were present in the sinusoids adjacent to the infarcts and areas of necrosis (Fig. 3).

Kidney: Both kidneys were extremely congested. The right weighed 350 grams and the left 450 grams, respectively. The capsules stripped with ease and in the right kidney there were numerous areas of yellowish subcapsular necrosis. On cross section they exhibited extremely edematous cortices (measuring 1.1 cm.) and well-demarcated columns of Bertini. The cortices were reddish with splotchy discoloration, and multiple areas of cortical necrosis were present. The medullas were conspicuous as a reddish-tinted striated area and again there were several areas of medullary necrosis. Both pelves were filled with blood and it was noted that no well-defined infarcts were found. No thrombi were noted in the renal vessels. The ureters were dilated and edematous and their mucosa was generally hemorrhagic.

Fig. 4.—The microscopic kidney. (Armed Forces Institute of Pathology, Picture No. 53 4978.) (×147. Reduced one-fifth.)

Microscopic sections showed uniform cloudy swelling of all tubules with large heme casts in the great majority of the distal convoluted tubules. The adjacent tubular epithelium was necrotic and the surrounding interstitial tissue contained collections of inflammatory cells spread both diffusely and in many cases focally into abscess formations. The glomeruli were bloodless and contained fused lobules. In many of the dilated Bowman's spaces there were coagulated fluid and red blood cells. The parietal Bowman's capsule was alternately proliferative and degenerative. In some instances there was evidence of regeneration of the distal convoluted tubules (Fig. 4).

Pituitary: The pituitary gland was enlarged measuring, 1.3 by 0.9 by 0.8 cm. and appeared to be incarcerated in the sella turcica. On section it was found to be friable, necrotic, yellow in color, and had areas of hemorrhage at the periphery. The posterior lobe appeared normal. Microscopic sections revealed a complete infarction necrosis associated with superficial hemorrhages of the anterior lobe (Fig. 5).

In summary the pathological findings were consistent with a severe pre-eclampsia and a severe lower nephron nephrosis in addition to which the entire anterior pituitary gland had been destroyed by necrosis. The edema and congestion usually noted in a toxemia death were present but to a very minor degree.

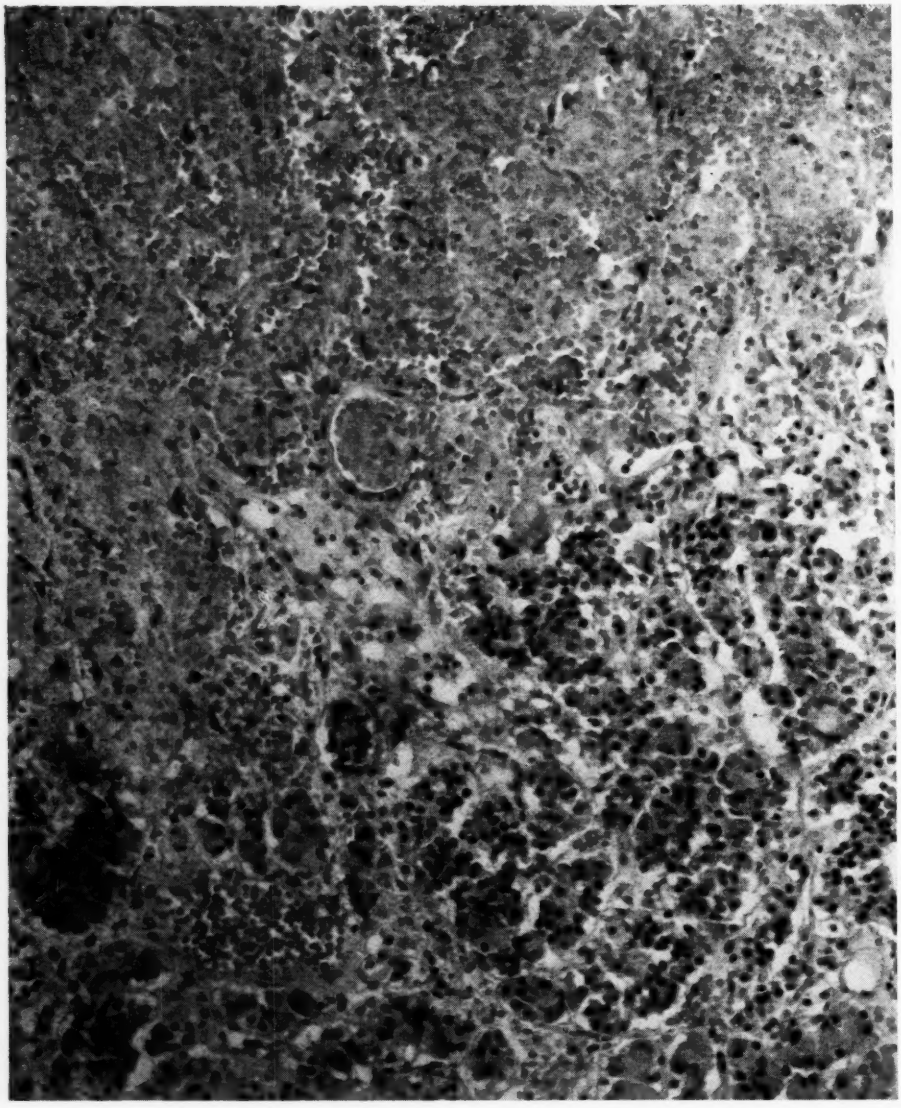


Fig. 5.—The pituitary gland exhibiting complete infarction necrosis associated with superficial hemorrhages of the anterior lobe. (Armed Forces Institute of Pathology, Picture No. 53 10481.) (×245. Reduced one-third.)

Comment

This was one of a group of toxemia patients treated in our hospital with the cation exchange resins. A full account of this therapeutic venture will be

published in a forthcoming article and need not be further amplified here. The acute severe intravascular hemolysis could not be fully explained except by postulating some unidentified toxin being suddenly released into the circulation as suggested by Young and McMichael[3] and the Smiths.[15, 16] A similar intravascular hemolytic accident reported recently by Kistner and Assali[17] was also inadequately explained as to etiology. Certainly the resin could not be incriminated as it was never absorbed from the intestinal tract. Potassium imbalance might very well have resulted from the acute breakdown of red blood cells[18] but as was definitely proved by several flame photometer analyses of blood serum it never did materialize. The acute renal insufficiency was immediately recognized and adequate conservative measures were initiated promptly to combat the anuric state.[11, 12] At no time during the period of therapy were the lung fields noted clinically to contain any perceptible edema nor was edema clinically manifest in any important quantity elsewhere. This lack of edema was conceded to be due to the excellent response to the Carbo-Resin therapy as well as to strict adherence to fluid replacement as recommended by Strauss[11] for treatment of anuric states.

The electrolyte balance was maintained with the help of repeated flame photometer estimations of serum sodium and potassium and by observance of daily electrocardiograms for signs of potassium imbalance. It was felt that either gastric suction or resin therapy or both would have helped to combat hyperkalemia if it had developed.[13] The serum potassium at no time during life exceeded 7.5 meq. nor did the electrocardiogram reveal any definite changes suggestive of potassium intoxication. The icterus was never considered as a primary factor in the case as it was thought to be due almost entirely to severe intravascular hemolysis. The liver did enlarge to some extent but never appeared to be progressively increasing in size. During the time this patient was under treatment for acute renal insufficiency the prognosis was of necessity guarded as the complete extent of kidney damage was unknown. Recovery would depend upon the length of time the patient remained anuric.[6] A diuresis ensuing prior to the tenth day usually forecasts a favorable prognosis in such cases.[6] However, autopsy revealed that the kidneys in this case had suffered irreparable damage as did the liver and other organs. The lungs were noted to be quite remarkably dry and bore witness to very good management of fluid balance. These patients are also prone to suffer damage to the anterior lobe of the pituitary gland as a result of acute anoxia. The end result is an infarction necrosis and a symptom complex described as Sheehan's syndrome.[10] This condition was a postmortem finding in this case and it was the opinion of everyone concerned that cortisone and glucose given in adequate daily dosage probably prevented severe electrolyte imbalance and hypoglycemia and thus prolonged this patient's life. Recovery under these circumstances would have been highly improbable. In retrospect, it is conceded that we might have instituted gastric suction early in this case as a means of relieving the progressively developing distention as well as affording some means of control over the slowly rising serum potassium.[13] The periportal hemorrhagic liver necrosis is of course identical with that found in most eclamptic livers and

we would be justified on this basis alone in classifying this case as one of non-convulsive eclampsia. The death undoubtedly resulted from the severe irreversible damage inflicted on the anterior pituitary but must be ultimately charged to severe pre-eclamptic toxemia. The initial renal shutdown may have been produced by the uterorenal reflex causing cortical ischemia with all of the subsequent pathological changes as suggested by Sophian[9] but such a train of events has as yet never been proved to occur in the human kidney as has been repeatedly stated by Chesley and McCaw.[19] In this reported case we are certain the etiology was severe prolonged shock due to the acute intravascular hemolysis that resulted in a severe hemoglobinemia and hemoglobinuria terminating in lower nephron nephrosis, bilateral cortical necrosis, complete anterior pituitary necrosis, and death.

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THE TREATMENT OF STRESS INCONTINENCE IN THE FEMALE*

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STRESS incontinence in the female has been an intriguing and complex problem to physicians for many years. It was in 1883 that Pawlik first suggested a plan of treatment for this condition by angulation of the urethra and narrowing of the lumen. During these past seventy years many methods of treatment have been advocated, mostly operative, and some nonoperative in character. The results obtained have been variously estimated to be from 100 per cent to 50 per cent of cures or lower.

In order to evaluate the various methods of treatment of stress incontinence in the female, it is essential to have a thorough and complete understanding of the anatomy of the female urethra and its associated structures. Also, a knowledge of the physiology of continence and the pathological physiology of incontinence is necessary to make an accurate diagnosis and plan for treatment.

The purpose of this study is to examine the more commonly accepted methods of treatment in usage today rather than to discuss the basic anatomy and pathology present, assuming that the diagnosis of stress incontinence has been accurately made.

Stimulated by the favorable reports of new operative techniques in 1948 and 1949, an analysis was made of the patients who were admitted for stress incontinence to the Division of Obstetrics and Gynecology at the Pennsylvania Hospital, Philadelphia. A critical study was made of the patients entering the hospital for this condition from 1942 to 1949. The results are shown in Table I.

TABLE I. OPERATIONS FOR STRESS INCONTINENCE, DIVISION OF OBSTETRICS AND GYNECOLOGY, PENNSYLVANIA HOSPITAL, 1942-1948

Total number of operations			20
Kelly plication		5	
Kennedy operation		2	
Anterior colporrhaphy		13	
Combined with posterior colpoperineorrhaphy	11		
Results			
Complete cure of stress incontinence	10	(50%)	
Improved	1	(5%)	
Failure	9	(45%)	
Complications			9
1. Postoperative difficulty of urination		3	
2. Complete incontinence		1	
3. Vesicovaginal fistula		1	
4. Postoperative hemorrhage		1	
5. Cystitis		3	

It can be seen from Table I that the number of patients operated upon for stress incontinence during this seven-year period is small, only 20 cases being

*Read at a meeting of the Obstetrical Society of Philadelphia, March 5, 1953.

reported. The results are considered poor, being only a 50 per cent complete cure of stress incontinence. One of the patients was improved (5 per cent) while 9 cases (45 per cent) resulted in failure. Upon a study of the type of operations performed, the failures were found to be due in most cases to an improper operative procedure. No doubt these failures were the result of a lack of understanding of the basic anatomy of the female urethra, the bladder, and the anterior vaginal wall, and to a failure in the understanding of the pathology involved in stress incontinence. The use of the anterior colporrhaphy operation, for example, resulted in a cure of the attending cystocele, but did not replace the bladder neck up behind the symphysis and restore the urethra to its normal position for continence. It can be seen that the number of complications in this small number of patients was serious.

With this study in mind, an effort was made to encourage the members of our Staff to make a thorough study of stress incontinence in the female and a new approach to the treatment. With the added stimulus of a report of the Millin-Read sling operation made by Read in Philadelphia in 1949, there was a reawakening of interest in stress incontinence in the female. During the past three years, 39 cases of stress incontinence have been operated upon by the author and his associates. These cases include those of Dr. Robert Kimbrough's Service at the Graduate Hospital of the University of Pennsylvania, and from the Division of Obstetrics and Gynecology of the Pennsylvania Hospital, as well as the Services of the author at the Philadelphia General Hospital and Delaware County Hospital, Drexel Hill, Pa.

The results and types of operation are seen in Table II.

TABLE II. RESULTS OF OPERATIONS FOR STRESS INCONTINENCE PERFORMED IN THE LAST FOUR YEARS

1. *Millin-Read (Sling) Operations, 1948-1952.*—		
Number of operations		14
Results: Cured of stress incontinence	14	(100%)
Complications:		
a. Postoperative obstruction	2	
b. Postoperative difficulty of urination	8	
c. Thrombophlebitis with pulmonary embolism	1	
d. Postoperative abdominal urinary leakage	3	
2. *Modified Marshall-Marchetti Suprapubic Vesicourethral Suspension Operations, 1949-1952.*—		
Number of operations		24
Results: Complete cure of stress incontinence	22	(91.66%)
Partial cure (75%) of stress incontinence (pre-existing neurological changes)	1	
Failure:	1	(8.33%)
Complications:		
a. Postoperative obstruction	0	
b. Postoperative difficulty of urination	3	
c. Postoperative abdominal urinary leakage	0	
3. *Berkow Paraurethral Fixation Operation.*—		
Number of operations		1
Result: Complete cure of stress incontinence	1	(100%)
Complications: None		
Total no. of operations, 1948-1952		39
Complete cures	37	(94.8%)
Partial cure 1 } Failures		
Failure 1 }	2	(5.2%)

An analysis of the results from 1948 to 1952 shows 37 out of 39 patients completely cured (94.8 per cent). The interval since operation is from 5 months to 2½ years. Two patients failed to achieve a complete cure of stress incontinence and are listed as failures. One of these patients deserves mention in that she has achieved a 75 per cent relief from stress incontinence. This patient was a 32-year-old white woman, para iii, who was operated upon 6 months previously in another hospital for hemorrhoids under spinal anesthesia. Following this operation she developed saddle anesthesia, probably as a result of the spinal anesthestic. At the time of operation upon her for stress incontinence in our hospital, a modified Marshall-Marchetti vesicourethral suspension operation was performed. Despite the neurological changes that the patient still shows, she has improved greatly in her relief of stress incontinence. Only on rare occasions is there a loss of urine during sneezing, coughing, or laughing. In retrospect, we believe that a sling operation, such as the Millin-Read procedure, would have been preferable and would probably have given a better result, due to the upward pull of the urethra by the rectus fascial strips which are uninfluenced by the anesthetic changes in the patient. The one complete failure recorded was in a patient who had a Marshall-Marchetti vesicourethral suspension performed in the routine manner without complications. She was perfectly continent until 6 weeks after operation at which time her symptoms recurred. No apparent reason can be found for the failure of the operation.

In presenting a review of the operations performed by me and my associates during the past three years, certain impressions of the operative treatment may be stated, as a result of the experiences gained in these procedures.

The Millin-Read sling operation has given very good results in the small number of cases in which we have used this technique. The operation is not easy. The straps of fascia from the rectus muscles for the sling are not difficult to make, but the placement of the sutures beneath the urethra from one side to the other is sometimes very difficult to perform. This is especially true if the patient has had one or more previous plastic operations for the relief of stress incontinence. The presence of scar tissue will frequently make it very difficult to "break through" this area to bring the fascial strips to the opposite side. Sometimes great force must be used even with the special Millin-Read instrument. Lacerations of the urethra may easily occur if this difficulty is encountered and we believe that upon two occasions we have torn the urethra in this area.

Postoperative difficulties of urination seem to be greater with this operation than with the other types used. In two of our cases, using this method, postoperative urinary obstruction occurred. It was necessary to relieve the obstruction in one by opening up the anterior vaginal wall and cutting the strips as they passed beneath the urethra. This resulted in a relief of the patient's obstruction and at the same time there was no recurrence of the stress incontinence. In the other patient who developed postoperative obstruction, it was necessary to perform a suprapubic cystotomy with eventual recovery and cure.

The operation, however, possesses a number of strong assets:

1. The end results achieved are usually very good. No failures occurred in our group of stress incontinent patients that had Millin-Read operations performed upon them.

2. The anatomic replacement of the bladder neck and urethra up behind the symphysis pubis is sound. Cystograms taken upon these patients after the Millin-Read sling operation show the bladder neck and urethra to be replaced in the normal position, with the normal posterior urethrovesical angle present, and with the disappearance of funneling of the bladder neck.

The Marshall-Marchetti vesicourethral suspension operation is not difficult to perform, and therefore I believe that it should be used more generally by surgeons and gynecologists. The results achieved, too, are generally very good. The complications, at least in our hands, were fewer than with the Millin-Read sling operation. One difficulty may be encountered in the operation. If the periosteum of the symphysis is thin or friable, the sutures may tear through the periosteum and make the operation difficult to perform. Such cases could result in failure.

We have modified the original Marshall-Marchetti operation by placing the sutures only from the vagina to the periosteum of the symphysis, being careful to avoid placing the sutures through the urethra as Marshall and Marchetti originally described. We believe by this modification that there is less chance of postoperative urinary leakage, less edema of the urethra, and, consequently, micturition is easier in these patients postoperatively.

The technique that we use is to place four or five sutures just lateral to the urethra in the vagina and anchor them to the periosteum of the symphysis in an ascending manner, the lowermost suture first being placed opposite the external urinary meatus through the vaginal wall and to the lower border of the symphysis. Succeeding sutures are then placed upward in the vagina and are anchored in an ascending manner on the periosteum of the symphysis until the last suture is tied at the top of the pubes. Two sutures are then placed through the muscularis of the bladder and anchored to the symphysial articulation. The results achieved in this manner are good, as will be seen in Table II.

Thirty-one of the 39 patients operated upon by our services from 1948 to 1952 had previous vaginal operations for the relief of their stress incontinence. The remaining 8 patients had no previous vaginal work performed, but did not show sufficient relaxation of the anterior wall or urethra to justify any vaginal procedure. Consequently, these patients had either the Millin-Read sling operation or the Marshall-Marchetti operation performed as the primary operation. All eight patients achieved a successful result for the relief of stress incontinence.

We have had no experience with the Aldridge or the Studdiford operation, but they have seemed to us to be quite complicated, and involving more operative work than is necessary. This also is true with Ball's operation of combined vaginal and abdominal plication with cystopexy.

If the vaginal portions of the Aldridge, Studdiford, or Ball operations are advocated as a reconstructive procedure essential in every case, and indispensable to the success of the sling operation, then this can be denied from experience alone. A number of patients with severe stress incontinence have been seen and successfully treated in whom there was no localized sagging of the anterior vaginal wall due to urethrocele or cystocele.

If, however, the vaginal portions of these operations are for the cure of a cystocele or urethrocele, as well as making the tunnel for the slings, then the procedures have merit.

Our experience in patients with cystocele and urethrocele accompanied by stress incontinence would indicate to us repair of the anterior wall with the Kennedy plication, perhaps followed by vesicourethral suspension.

No definite or final pronouncements can be made on the subject of the relief of stress incontinence in the female, for the problems of this condition are not as yet completely solved. However, we believe certain answers can be given to the question of nonoperative and operative treatment. In general, this must be determined in accordance with practice and results. At the present time the problem is still under intensive study. Based on our experience, we have adopted the following approach to treatment of stress incontinence:

1. In patients who present themselves primarily with symptoms referable to stress incontinence of varying degrees, we believe that they should initially have the benefit of nonoperative treatment through the use of the physiological exercises, and the use of the perineometer, if necessary. Kegal and his associates have reported such excellent results that we have instituted this method on our services in the hope that it may be successful in preventing operation, or, if not, to prepare the patient better for surgery. For the past six months we have instituted the use of physiological exercises to strengthen the pubococcygeus muscle with the use of the perineometer. Our results so far are not well defined; certain patients have achieved some relief. In the ones in whom little or no result has been obtained with the exercises we believe that it is due to a lack of conscientious effort on the part of the patient. The experiences are too new for us to evaluate properly, but we believe that this method is a very definite and helpful approach to the problem.

2. Patients who present themselves primarily with symptoms referable to prolapse of varying degrees and in whom stress incontinence is not emphasized, but ascertained upon routine history and physical examination, should have either a Manchester type of operation or a vaginal hysterectomy performed, with the addition of certain technical procedures carefully performed for the reestablishment of vesical and urethral control. Specifically, this means replacing the bladder neck and urethra up behind the symphysis pubis. This is done either by the method of the Kennedy plication technique, or by the use of plication with added support from suturing of the pubococcygeus muscles or the bulbocavernosus muscles, after the technique of Sundberg.

3. In patients who present themselves with stress incontinence as the primary symptom and who are seeking our services for its relief, a vesicourethral

suspension or sling operation should be performed or added to whatever vaginal procedures may be necessary. These patients are usually those who show a moderate cystocele or urethrocele or varying degrees of uterine prolapse. The necessary vaginal repair is carried out using the Kennedy, or Kelly-Te Linde plication technique, or the Manchester type operation followed by a sling operation or vesicourethral suspension. It is in these patients that the Aldridge or Studdiford sling operation could also be used.

4. A vesicourethral suspension operation or sling operation should be the procedure of choice in patients who have undergone previous vaginal operations for the relief of stress incontinence, and in whom, though the anatomical result has been good, the establishment of continence has failed.

5. A primary suprapubic operation such as the vesicourethral suspension or Millin-Read sling operation should be performed in those patients in whom there is no real degree of anatomic deformity or displacement (cystocele or urethrocele) and yet stress incontinence is present and distressing. A posterior colpoperineorrhaphy, if indicated, may be performed in these patients, based upon the findings of Davies, and others, if necessary, but no anterior vaginal wall repair should be done.

6. In patients with stress incontinence, with a prolapsus of the uterus, and in whom hysterectomy is warranted, a vaginal hysterectomy should be performed. The removal of the uterus should be followed by a plication of the urethra and bladder, and the suturing of the round and broad ligament stumps securely up behind the symphysis to the periosteum, for the relief of stress incontinence.

7. In those patients in whom an intraperitoneal procedure is indicated, such as hysterectomy for fibroids, etc., a suprapubic vesicourethral suspension or a sling operation can be conveniently combined with the ordinary intra-abdominal operation, with benefit and relief of the stress incontinence.

Summary

Each patient must be carefully evaluated as to the etiology of the incontinence, and the decision for operative intervention is made only after the conservative or nonoperative treatment fails. Then the type of operation chosen will depend upon the age of the patient, the pathologic anatomy present, the previous operative work performed, and last, but not least, the skill and technique of the surgeon. Much has been done on the etiology, diagnosis, and treatment of stress incontinence in the female. Much more work needs to be done before all the problems of stress incontinence are solved.

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POSTEPISIOTOMY PAIN CONTROL WITH EFOCAINE

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DURING the last three decades, tremendous advances have been made in the development of safer methods for the control of pain associated with labor and delivery. In contrast, comparatively little effort has been directed toward improving palliative measures for the relief of postepisiotomy pain, although it is a major source of postpartum discomfort.

Attempts to minimize postepisiotomy pain by varying surgical technique have been disappointing.[1, 2] Prolonged local anesthesia is an obvious alternative method, but the anesthetic-in-oil solutions, which have been the only agents for this purpose available in the past, have been revealed as ineffective,[3, 4] and even dangerous.[5-7]

Recent reports[8-20] have described a new aqueous miscible, long-acting local anesthetic, Efocaine,* which has been used with a high degree of success in the control of postoperative pain. The water-insoluble anesthetic bases (procaine and butylaminobenzoate) in Efocaine are dissolved to the point of saturation in an aqueous miscible organic solvent composed of propylene glycol and polyethylene glycol-300. Upon injection of the solution, tissue fluids cause the anesthetic agents to precipitate as an in situ crystalline deposit. Absorption of the deposit is delayed by its low aqueous solubility, and its anesthetic action is thus prolonged for periods of time exceeding 6 days. A histopathologic study[21] has revealed that Efocaine does not encapsulate, cause neurodegeneration, nor interfere with wound healing. We became interested, therefore, in evaluating the preparation in the control of postepisiotomy pain.

Material and Methods

Although the recommended technique calls for deep subcutaneous or intramuscular injection, we decided to study, as well, the effects of Efocaine when injected more superficially. Our purpose was to determine what effects might be expected if a too superficial injection of the drug should occur inadvertently.

A consecutive series of postepisiotomy patients, all of whom had received continuous caudal analgesia for labor and delivery, were treated with Efocaine upon the completion of episiotomy repair. A dry syringe equipped with a 22 gauge, 1½ inch needle was used for the infiltration procedure. Three different injection techniques were used:

Group 1.—The initial group, consisting of 19 patients, was injected subcutaneously near the skin surface and along the edges of the episiotomy. Eight to 10 c.c. of Efocaine were used (Table I).

Group 2.—The second group, consisting of 4 patients, was injected with 5 to 9 c.c. of Efocaine about 2 cm. from the edges of the episiotomy, but still close to the skin surface (Table II).

*Efocaine for this study was supplied by E. Fougera and Company, Inc.

TABLE I. PATIENTS WHO RECEIVED EFOCAINE ALONG EDGES OF EPISIOTOMY (SUBCUTANEOUSLY)

CASE NO.	AMOUNT OF EFOCAINE INJECTED (C.C.)	MAJOR RESPONSES*		REMARKS
		TYPE	% OF DAYS OBSERVED	
1.	8	N	100	Edema due to procaine allergy (sloughing)
2.	8	N	66	
3.	10	S	66	
4.	10	T	50	Third-degree extension, late suppuration
5.	8	N	100	
6.	8	N	100	
7.	8	T	100	Sloughing on fourth postpartum day
8.	8	N	100	
9.	8	N	100	
10.	8	N	100	
11.	8	N	75	
12.	8	S	65	
13.	8	S	75	
14.	8	S	100	
15.	8	S	80	
16.	8	S	100	
17.	8	S	60	
18.	8	T	100	
19.	8	S	60	

*N, Not tender.
S, Slightly tender.
T, Tender.

Summary of Major Responses:

Not tender	8 patients (42.1%)
Slightly tender	8 patients (42.1%)
Tender	3 patients (15.8%)
Sloughing or purulence	3 patients (15.7%)

TABLE II. PATIENTS WHO RECEIVED EFOCAINE 2 CM. FROM EDGES OF EPISIOTOMY (SUBCUTANEOUSLY)

CASE NO.	AMOUNT OF EFOCAINE INJECTED (C.C.)	MAJOR RESPONSES*		REMARKS
		TYPE	% OF DAYS OBSERVED	
101	5	N	60	
102	5	S	60	
103	9	T	80	Sloughed
104	5	N	100	

*N, Not tender.
S, Slightly tender.
T, Tender.

Summary of Major Responses:

Not tender	2 patients (50%)
Slightly tender	1 patient (25%)
Tender	1 patient (25%)
Sloughing	1 patient (25%)

Group 3.—This group, which included 38 patients, was injected with 4 to 6 c.c. of Efocaine, 2 to 3 c.c. on each side of the episiotomy. The point of entry for the infiltration was made 1 cm. below the lower angle of the episiotomy and the needle was advanced upward to a point very close to the mucocutaneous junction. The needle was always kept 1 to 2 cm. from the edges of the wound, and deep in the perineal tissues (Fig. 1). Injection was made as the needle was withdrawn, and aspiration was carried out repeatedly to avoid introduction

of the material intravenously. Each patient received only one infiltration; in no case was infiltration repeated because of tenderness during the postpartum period (Table III).

The efficacy of the infiltration was estimated daily by palpation and pressure over the episiotomy. Tenderness elicited only upon deep pressure was rated "slight," and tenderness elicited upon slight pressure was rated "tender."

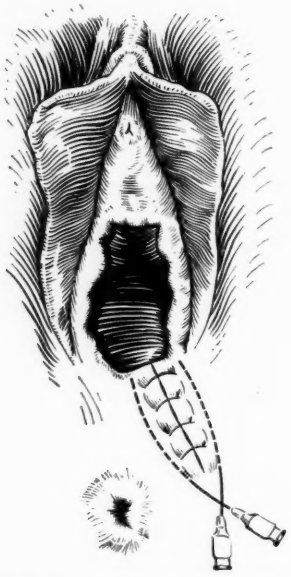

Fig. 1.—Technique of infiltration of Efocaine.

Results

The majority of patients enjoyed considerable relief of postpartum episiotomy discomfort following infiltration with Efocaine. A total of 61 patients were treated, and 53 (87 per cent) exhibited either no tenderness at all, a tenderness to only deep pressure, or else vacillated between these two responses from day to day during the observation period. Of the entire group, 21 patients (34.4 per cent) exhibited no tenderness to even deep pressure during all or most of the postpartum period, while for 32 patients (52.4 per cent) the major response was freedom from pain except to deep pressure over the episiotomy. Only 8 patients (13.1 per cent) were tender to slight pressure during most of the postpartum period. Two of these latter patients (3.3 per cent) persisted in being sensitive to slight pressure throughout the entire observation period, but they were members of one of the two groups which received a superficial injection of Efocaine contrary to the recommended technique (Table I).

In summary, 61 patients were tested for tenderness on each of a varying number of days following episiotomy. For all patients combined, a total of 288 daily tests to determine tenderness were made and of these 108 daily tests, or 37.5 per cent, resulted in an estimate of no tenderness, while for 133 daily tests,

or 46.2 per cent, the estimate was slight tenderness. In only 13 daily tests (16.3 per cent) did the wound area give evidence of sensitivity to just slight pressure. All the patients, many of them multiparas who recalled their previous experience, expressed the opinion that very definite relief was effected by the infiltration with Efocaine.

Infiltration of the drug too close to the skin surface was attended by a higher incidence of induration and sloughing (17.4 per cent) than occurred when the agent was carefully injected into the deeper tissues (7.9 per cent).

TABLE III. PATIENTS WHO RECEIVED EFOCAINE DEEP IN PERINEAL TISSUES ON BOTH SIDES OF EPISIOTOMY

CASE NO.	AMOUNT OF EFOCAINE INJECTED (C.C.)	MAJOR RESPONSES*		REMARKS
		TYPE	% OF DAYS OBSERVED	
201	6	N	75	
202	5	S	65	Hemorrhoid tender
203	5	S	75	
204	4	N	100	
205	4	N	75	
206	5	S	65	
207	5	N	100	
208	5	N	75	
209	5	N	75	
210	5	S	60	
211	5	S	100	Hemorrhoid tender
212	5	N	100	
213	5	T	50	
214	5	N	75	
215	5	S	80	
216	5	S	100	
217	5	S	66	
218	5	S	80	
219	5	S	66	
220	5	T	66	Induration and sloughing
221	5	S	57	
222	5	S	85	
223	5	S	50	
224	5	S	80	
225	5	S	66	Induration and sloughing
226	5	S	66	
227	5	S	100	
228	5	S	100	
229	5	S	55	
230	5	T	55	
231	5	S	55	Induration and sloughing
232	5	S	50	
233	5	S	40	
234	5	N	100	
235	5	N	100	
236	5	S	66	
237	5	T	80	
238	5	N	75	

*N, Not tender.
S, Slightly tender.
T, Tender.

Summary of Major Responses:

Not tender	11 patients (28.9%)
Slightly tender	23 patients (60.5%)
Tender	4 patients (10.6%)
Sloughing	3 patients (7.9%)

Except for these cases, and one wherein the patient exhibited a procaine allergy, there were no local or systemic toxic effects.

The results of the study are summarized in Tables I, II, III.

Discussion

Effective control of postepisiotomy discomfort can contribute importantly to the successful management of the postpartum patient. A patient not burdened with pain generally eats well, sleeps better, and is more likely to have a good morale and to enjoy the benefits which are derived from it. Our investigation has demonstrated that Efocaine is capable of controlling postepisiotomy pain during the first 3 to 7 postpartum days.

The administration of Efocaine is easily accomplished by deep (1 cm.) infiltration of 2 to 3 c.c. of the solution as a fine line on each side of the wound. It is important that the Efocaine not be injected too superficially nor nearer than 1 cm. to the edges of the episiotomy. The crystalline material formed in situ when Efocaine is injected will tend to grate upon the tissues if it is located too superficially, and skin erosion may result. Pooling of the agent at any one site results in a clump of crystals and can lead to similar effects. Both superficial placement and pooling also deprive Efocaine of its maximum anesthetic action.

Caution against injecting Efocaine too close to the edges of the episiotomy is necessitated by the hypertonic nature of the preparation. Because it is hypertonic, Efocaine will withdraw tissue fluid to the site of the injection, an action which is usually of no consequence, but which can lead to a breakdown unless injection is sufficiently removed from the already edematous area immediately surrounding the episiotomy wound.

The noteworthy relief of postepisiotomy pain afforded by Efocaine makes it extremely desirable for such a purpose. The simplicity of both the equipment and technique of administration makes Efocaine available for use by all obstetricians under any operative conditions. We recommend the use of this agent in the manner described above and in the doses noted for the control of perineal distress following episiotomy.

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PREGNANCY AND HODGKIN'S DISEASE

A Report of Eight Cases

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A REVIEW of the literature reveals a comprehensive article by Kasdon[1] in which 24 known cases of pregnancy complicating Hodgkin's disease are reported. He adds case reports on three additional patients.

Since Kasdon's report, 10 additional articles on this subject have appeared, some reporting actual cases, others alluding in a more general way to experiences with a limited number of patients. The most recent articles are those of Stewart and Monto,[2] and Hennessy and Rottino.[3] The cases they record bring the total number of reported cases to 65.

In the Prenatal Clinic at Walter Reed Army Hospital, a total of 8 confirmed cases of Hodgkin's disease complicating pregnancy have been seen in the past six years. During this period there have been 7,822 deliveries, making the incidence of Hodgkin's disease in pregnancy in this clinic 0.97 per 1,000 deliveries. We feel that the rarity of this complication in pregnancy warrants the reporting of these cases and the presentation of two of the cases recorded in Table I, in one of which nitrogen mustard was used.

CASE 5.—A 26-year-old patient, white, gravida i, para o, was first seen in the Walter Reed Army Hospital Prenatal Clinic on March 9, 1951. Her past history revealed an admission to this institution on Jan. 23, 1950, because of a swelling in the neck of eight months' duration. She had noted dysphagia and increasing fatigability. There was a 4 by 6 cm. nontender, firm, nodular mass on the anterior surface of the neck to the left of the midline which did not move with swallowing; a freely movable 2 to 3 cm. mass under the left side of the mandible; another, also freely movable, in the anterior cervical area on the right, and two small nodular masses situated bilaterally in the supraclavicular region. A 2 cm. mass was also noted in the left axilla. She received the following treatment:

12 x-ray treatments from 2/2/50 to 2/17/50, as follows:

1. Anterior mediastinum	2,400 r (skin) 1,440 r tumor dose

20 x-ray treatments from 3/3/50 to 4/29/50 as follows:

1. Right cervical	2,400 r (skin)
2. Left supraclavicular	2,400 r (skin)

15 x-ray treatments from 5/13/50 to 6/20/50 as follows:

1. Left axilla	2,100 r (skin)
2. Right axilla	2,100 r (skin)

7 x-ray treatments from 7/8/50 to 7/22/50 as follows:

1. Submental	2,600 r (skin)

14 x-ray treatments from 9/2/50 to 9/21/50 as follows:

1. Right axilla	2,100 r (skin)
2. Left axilla	2,100 r (skin)

10 x-ray treatments from 10/30/50 to 11/10/50 as follows:

1. Left cervical	3,000 r (skin)

On Jan. 26, 1951, a biopsy of a node in the neck revealed Hodgkin's granuloma (lymphogranulomatosis) (Fig. 1). Examination for other tumor masses was negative. Radiation therapy, as recommended by the Tumor Board, consisted of a total of 2,400 roentgen skin doses given directly over the thyroid gland over a two-week period. There was dramatic decrease and no ill effects resulted from the radiation. She was given two weeks' rest and another 2,400 roentgen skin dose over the left supraclavicular node. Twelve x-ray treatments were given between Feb. 2 and Feb. 15, 1951. She received 2,400 r on the skin of the anterior mediastinum, a total tumor dose of 1,440 r in 16 days.

A chest film on Jan. 29, 1951, revealed a keystone-shaped homogeneous density in the superior mediastinum, and a slight increase in the pulmonary conus segment, but was otherwise noncontributory. A repeat chest x-ray on March 9, 1951, showed the chest to be normal.

On admission, April 17, 1951, the patient was placed on toxemia regime and the blood pressure returned to normal. Labor was medically induced, and she was delivered spontaneously of a 6 pound, 3 ounce normal female infant on April 19, 1951.

This patient's postpartum course was uneventful except that her efforts at regaining strength were considerably retarded as compared to those of other patients of similar age and parity. She was discharged from the hospital in care of the Out Patient Clinic.

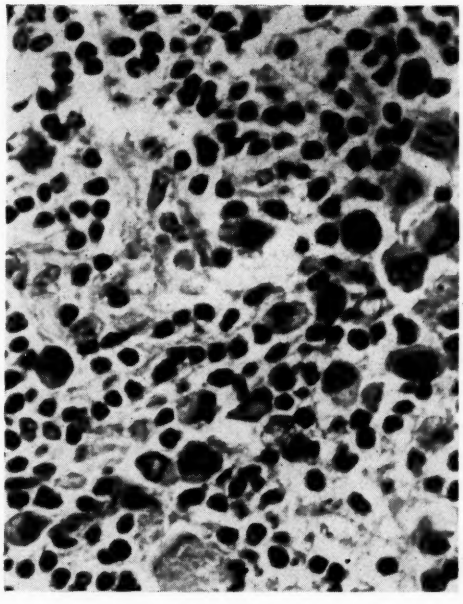

Fig. 1 (Case 5).—Photomicrograph of lymph node from neck showing lymphogranulomatosis.

She has been followed by the Radiation Therapy Section for the past 18 months. When she was examined on April 30, 1952, a single 2 cm. node was discovered in the left axilla. The patient stated that this node had enlarged slightly within the previous few months. A second small node was noted in the left axilla and one in the right. Each node was about 1 cm. in diameter. She appeared well, her weight was stationary, and a chest x-ray was normal. No further therapy was given.

TABLE I. REPORT OF 8 CASES OF PREGNANCY IN HODGKIN'S DISEASE

NO.	YEAR	AGE AND PARITY	TIME OF DIAGNOSIS	MODE OF DELIVERY	TREATMENT	COURSE AND OUTCOME	POSTPARTUM COURSE	INFANT
1.	1947	22 Grav. i Para 0	7th month of pregnancy	Low forceps vaginal	Irradiation	Remission	Uneventful	Normal
2.	1949	24 Grav. ii Para i	See above	Low forceps vaginal	Irradiation prenatally	Remission	Not known	Normal
3.	1951	31 Grav. i Para 0	5th month of pregnancy	Spontaneous vaginal	Irradiation prenatally	Remission	Uneventful	Normal
4.	1952	32 Grav. ii Para i	5th month of pregnancy	Due March 19, 1953	None so far this pregnancy	Possible early exacerbation	Undelivered	-------
5.	1950	26 Grav. i Para 0	15 months before delivery	Spontaneous vaginal after medical induction	Irradiation	Remission	Uneventful	Normal
6.	1949	21 Grav. i	13 months before delivery	Low forceps after medical induction	Irradiation	Recurrence. Irradiation therapy with remission	Uneventful	Normal
7.	1951	31 Grav. i Para 0	1st month of pregnancy	Due Sept. 23, 1951	Nitrogen mustard	Remission followed by exacerbation	Uneventful	Normal
8.	1951	32 Grav. ii Para i	24 months prior to pregnancy	Spontaneous vaginal Sept. 1, 1951	None. X-ray therapy 2 years before pregnancy	No evidence of disease when last seen	Uneventful	Normal

CASE 7.—A 27-year-old woman, gravida ii, para i, was hospitalized at Walter Reed Army Hospital from Dec. 13, 1950, to Jan. 13, 1951, for treatment of Hodgkin's disease. Sept. 23, 1951 was given as her expected confinement date. During her hospitalization in January, 1951, examination revealed rather extensive retroperitoneal lymphadenopathy with involvement of breast and thorax and moderate anemia. A biopsy revealed a Hodgkin's disease node in the upper outer quadrant of the left breast (Fig. 2). Because of the wide dissemination of the disease, systemic treatment was agreed upon.

She received her first course of nitrogen mustard, 19.25 mg. intravenously over a four-day period, starting Jan. 5, 1951. She was readmitted Feb. 12, 1951, and a diagnosis of pregnancy of approximately one month's duration was made.

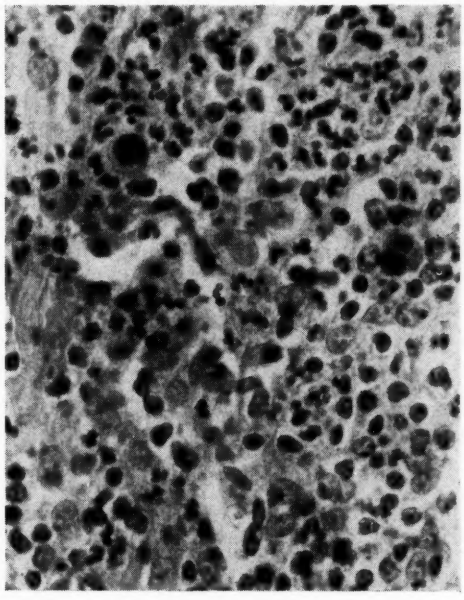

Fig. 2 (Case 7).—Photomicrograph shows Hodgkin's disease in node removed from breast.

The remainder of the prenatal period was uneventful. The hematocrit remained within normal limits. The patient first felt fetal movement on May 5, 1951. No further progress of the disease was noted. She delivered a full-term living infant on Oct. 10, 1951. The labor and immediate postpartum period were well within normal limits. She was seen as an outpatient on Nov. 1, 1951 because of abdominal pain and was admitted with a diagnosis of Hodgkin's disease in exacerbation, endometritis, and subinvolution of the uterus. Routine therapy produced good results. Another course of nitrogen mustard was given shortly after admission and she was discharged as improved.

On Jan. 30, 1952, she was readmitted with severe right flank and right lower quadrant pain, the etiology of which was said to be nephroptosis, secondary to perirenal involvement by Hodgkin's disease. She required almost constant sedation until a third course of nitrogen mustard was administered. This was followed by a remission.

This patient was readmitted two months later in May, 1952, with further progression of the disease and severe pain, and required constant sedation. Because of amenorrhea which had persisted since January, 1952, a pelvic examination was made and normal female genitals were found. It was postulated that the amenorrhea was secondary to x-ray therapy given to the lumbosacral area in February.

Shortly thereafter, against advice, she requested release and returned to her family in Wisconsin and further follow-up was, therefore, no longer possible. The infant was said to be living and well at the time of discharge.

Summary

1. Eight cases of pregnancy complicating Hodgkin's disease are reported.
2. These cases seem to indicate that fertility is not affected by this disease.
3. No cases were seen in which spontaneous abortion occurred.
4. There has been no evidence of hemorrhagic tendency in these patients.
5. All of these cases occurred in women between the ages of 21 and 32 years.
6. Pathological examination of the placentas revealed no abnormality.
7. No evidence was found to indicate that pregnancy caused specific increase or exacerbation of Hodgkin's disease.
8. Nitrogen mustard was used in treating one patient beginning in the first eight weeks of gestation. She was subsequently delivered of a normal viable infant following this therapy. The child is alive today.
9. There has been no evidence of radiation effect on any of the five infants born to mothers who had radiation therapy during pregnancy.

Conclusions

We concur with Kasdon's conclusions except that we have not had a patient in whom Hodgkin's disease has been transmitted from mother to fetus via placenta. The conclusions are as follows:

1. Hodgkin's disease does not grossly alter ovulation, fertility, incidence of spontaneous abortion, or obstetrical hemorrhage.
2. The incidence of obstetrical complications is not increased by coincidental Hodgkin's disease.
3. Kasdon states that Hodgkin's disease is transmitted from the mother to the fetus across the placenta in 9 per cent of the cases reported.
4. There is no evidence in the literature of injury to the shielded fetus from roentgen radiation used in the treatment of Hodgkin's disease.
5. Interruption of pregnancy during the course of Hodgkin's disease is not indicated from the evidence at hand.
6. Pregnancy apparently does not alter the course or progress of Hodgkin's disease.

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A FATAL CASE OF PULMONARY INFARCTION DUE TO EMBOLISM OF AMNIOTIC FLUID

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SINCE Steiner and Lushbaugh first reported 8 cases of maternal pulmonary embolism by amniotic fluid in 1941, and introduced a heretofore unrecognized complication of pregnancy, several additional cases have been reported.

This case, showing microscopic findings consistent with previously reported cases, is reported not only to add to the growing list of such diagnosed cases, but because the clinical picture is different in some respects from the majority of cases so far reported.

Case Report

Clinical History.—

A 20-year-old para i, gravida ii, Rh-positive white woman with an estimated date of confinement of Aug. 8, 1952, was admitted to the hospital at 1:40 P.M., June 11, 1952, because of slight painless vaginal bleeding which had started that morning. Her first child was delivered June 30, 1950, without complications. On admission she was at 32 to 34 weeks' gestation according to calculations from the last menstrual period (Nov. 1, 1951), but an abdominal x-ray diagnosed 8½ months' gestation (38 weeks). Fetal heart tones were present at 140 per minute in the left lower quadrant, the head dipping, and the blood pressure 110/78. The blood count and urinalysis were normal, Kahn test negative.

Labor commenced spontaneously at 2 A.M., June 12, 1952, and the first stage terminated at 9:30 P.M. The second stage terminated at 9:53 P.M. with the delivery, by low forceps, of a male infant, that weighed 2,072.5 grams, followed immediately by the placenta which was complete. Contractions were of the usual character throughout labor. The membranes ruptured spontaneously just prior to delivery and the amniotic fluid was sanguineous. The fetal heart tones were reported as present by the nurse while the doctor was scrubbing, but following delivery the infant did not breathe and was completely flaccid. No placental lacerations were noted. The bleeding was stated to be heavier than usual during the first stage, and the estimated amount at the end of the third stage was about 300 to 350 c.c. Anesthesia for the labor and delivery consisted of 50 mg. of Demerol and 1½ grains of Seconal given early in the first stage, and a saddle block using 2.5 mg. of Heavy Nupercaine, for the second stage and delivery.

The patient first complained of right chest pain of a mild character while the obstetrician was attempting to get the baby to breathe. The pain persisted and became rapidly worse. She became restless and coughed. This was nonproductive at first but rapidly changed to pink frothy sputum and râles could be heard in the right base. The blood pressure had dropped to 90/50 and before she left the delivery table a medical consultant had diagnosed pulmonary embolism and she was given 7½ grains of aminophylline intravenously, 100 mg. of Demerol, 20 mg. of Vasoxyl, and oxygen.

She responded somewhat and was moved to the ward, but at 1:15 A.M. June 13, 1952, she suddenly went into profound shock with imperceptible blood pressure and pulse, from

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which she did not recover. Therapy for the next 24 hours consisted of positive oxygen respirations, a total of 2,500 c.c. of whole blood, and various supportive measures as indicated. There was no postpartum hemorrhage, the lochia being described as normal. The patient demonstrated cyanosis, unconsciousness, involuntary bowel movements,

Fig. 1.

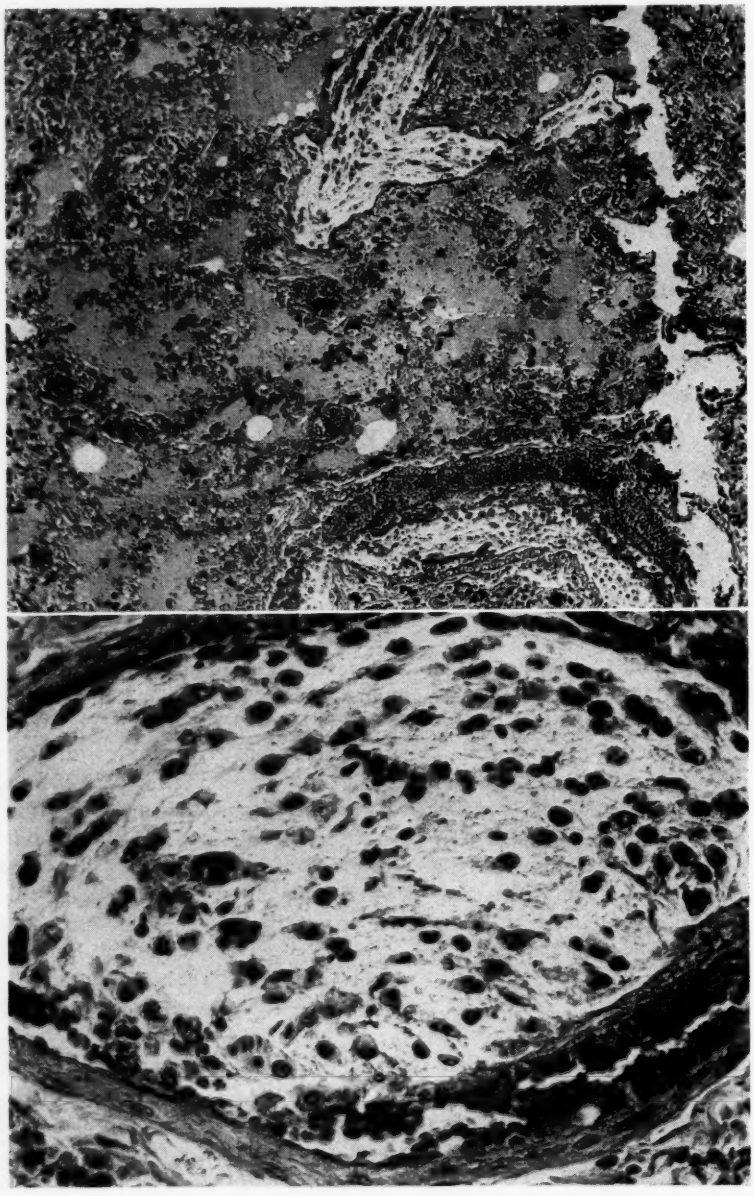

Fig. 2.

Fig. 1.—Lung, low power. Note the nonstaining amniotic fluid emboli in two arterioles. (The black dots in the surrounding lung tissue are formalin pigment.) (Hematoxylin and eosin stain. 16 mm. 0.25. Reduced one-third.)

Fig. 2.—Lung, high power. Higher magnification of amniotic fluid emboli in arteriole. Note stringy matrix with enmeshed cellular debris and neutrophils. (Hematoxylin and eosin stain. 4 mm. 0.65. Reduced one-third.)

vomiting, and anuria. At 10:00 A.M., 120 c.c. of grossly bloody urine was removed by catheter and showed albumin, casts, red and white cells. The temperature gradually rose to 103° F. and the patient died at 4:35 A.M., June 14, 1952, 30 hours and 42 minutes after delivery.

Gross Autopsy Findings.—

External: This was a slightly obese, dark-complexioned white woman who measured 161 cm. and weighed 150 to 160 pounds. There was no edema or jaundice.

Fig. 3.

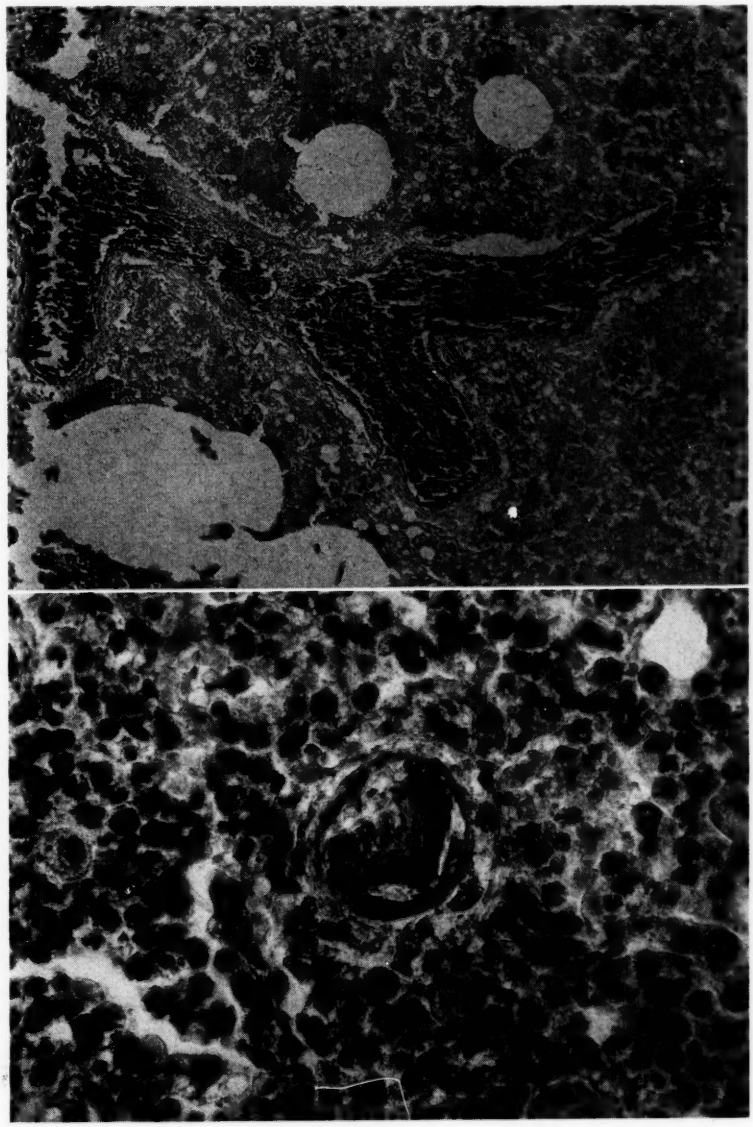

Fig. 4.

Fig. 3.—Lung, low power. Note large mucus content (dark red staining) of amniotic fluid emboli in arterioles. (Small black spots outside arteriole represent formalin pigment.) (Mucicarmine stain. 16 mm. 0.25. Reduced one-third.)

Fig. 4.—Lung, high power. Note dark-appearing masses of fatty material in small capillary. (Scarlet red stain. 4 mm. 0.65. Reduced one-third.)

Pleural cavities: The left lung weighed 430 grams, the right lung 450 grams. There was no free fluid. Both lungs were dark blue and indurated in the lower lobes and lower portions of the upper lobes, with multiple petechia in the pleura. The upper lobes were light red and crepitant. The line of demarcation was sharp. The cut surfaces were wet. The arterial tree was negative, bilaterally, as were the veins and bronchi.

Pericardial cavity: The heart weighed 280 grams and showed no gross abnormalities except for petechiae in the epicardium. The blood in the right auricle and pulmonary

Fig. 5.

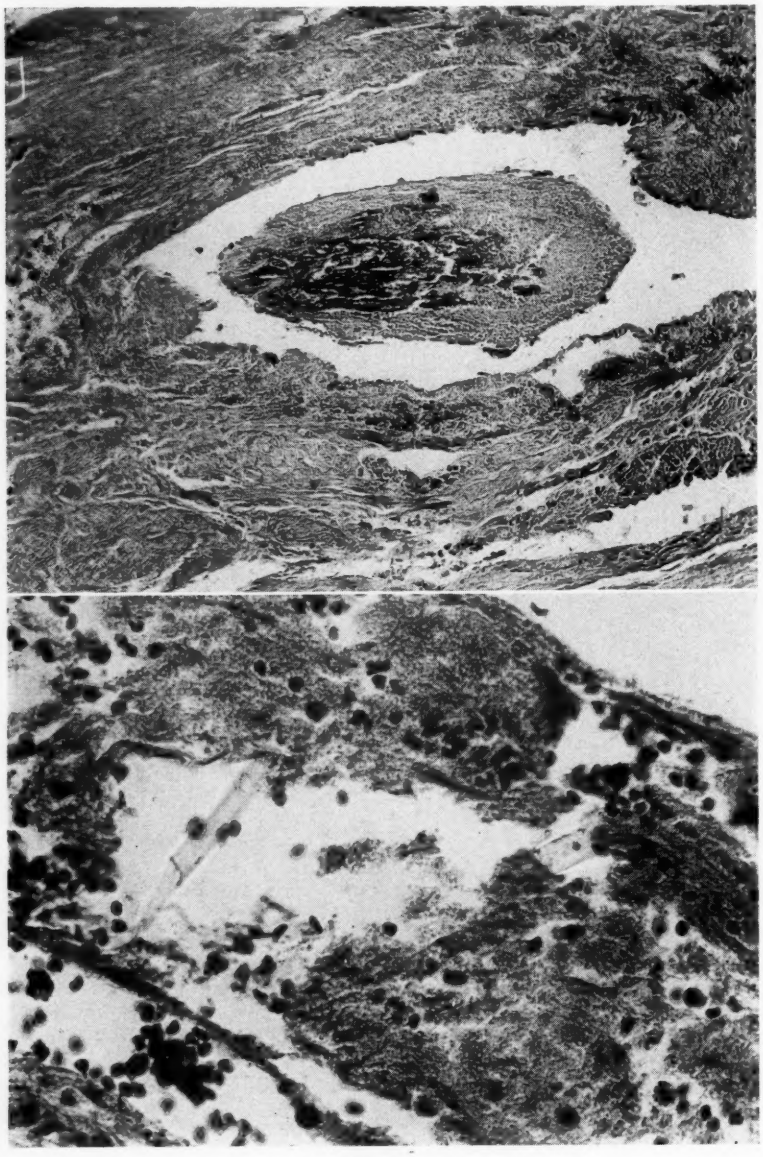

Fig. 6

Fig. 5.—Uterus, low power. Uterine sinus containing a thrombus with mucus (dark-appearing material) in the center. (Mucicarmine stain. 16 mm. 0.25. Reduced one-third.)

Fig. 6.—Uterus, high power. Uterine sinus filled with a thrombus in which are mucus and two lanugo hairs. (Hematoxylin and eosin stain. 4 mm. 0.65. Reduced one-third.)

artery was not frothy or clotted. There was 30 c.c. of straw-colored fluid in the pericardial cavity.

Abdominal cavity: There was no free fluid. The liver was not enlarged. It weighed 1,540 grams, and the cut surface was mottled red and tan with prominent lobules. There was no gross necrosis.

The pancreas, spleen, and adrenals were not remarkable.

The left kidney weighed 180 grams and the right 205 grams. The capsules contained numerous petechia. The external surfaces were smooth and the cut surfaces dark red and congested. The right ureter and pelvis were slightly dilated (the ureter 1 cm. in diameter) but no obstruction was present at autopsy.

The cervix and uterus weighed 1,120 grams and assumed the usual early postpartum appearance. There were interstitial hemorrhage and small lacerations in the cervix. The endometrium was ragged and hemorrhagic, but there were no large lacerations. The placental attachment had been on the right anterior wall of the fundus. The dilated uterine sinusoids and the broad ligament veins were filled with antemortem blood clots.

The intestines showed petechial hemorrhages in the mucosa, and the cecum and rectum contained recent mucosal ulcerations. The fecal content was normal.

The brain weighed 1,150 grams and was not remarkable.

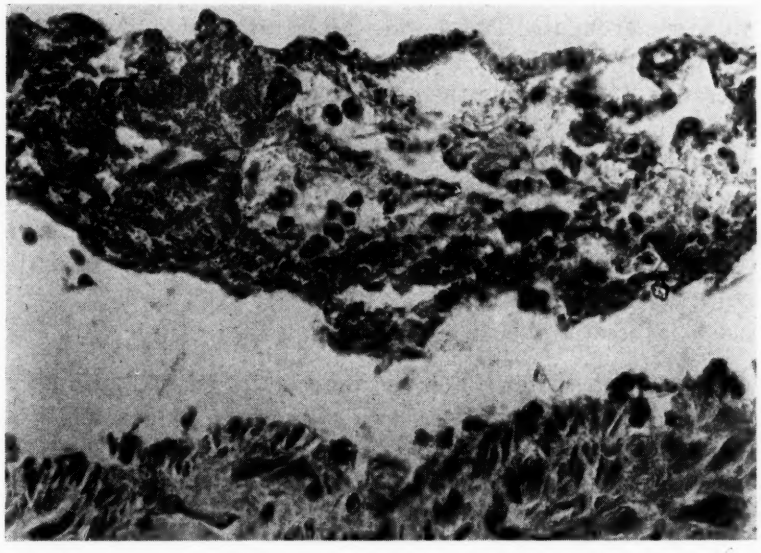

Fig. 7.—Broad ligament vein, high power. Mucus, leukocytes, and cellular debris within a thrombus. (Hematoxylin and eosin stain. 4 mm. 0.65. Reduced one-third.)

Microscopic Autopsy Findings.—

Lungs: Many of the small arteries and capillaries, from both the lower and upper lobes, were dilated with the typical, nonstaining (with hematoxylin and eosin) foreign material characteristic of amniotic fluid. These emboli did stain with mucin and fat stains, however, and contained cellular debris, many neutrophils, and occasional epithelial squamae, lanugo hairs, and vernix caseosa (Figs. 1, 2, 3, and 4). Some of the vessels showed this material in the center of embolic blood clots. The surrounding lung tissue from the bases showed hemorrhagic infarction. There was no foreign body reaction, mobilization of macrophages, or arteritis around the emboli.

Liver: The liver showed central necrosis of recent origin and was negative for emboli.

Kidneys: The kidneys showed congestion and edema and tubular casts. There was a mild healed pyelonephritis in the right. They were negative for emboli.

Uterus and cervix: These organs both contained thrombi in the sinuses in the center of which were the same elements of amniotic fluid as seen in the lungs. The broad ligament veins were similar (Figs. 5, 6, and 7). All these emboli took the special stains mentioned above.

Cecum and rectum: These organs showed mucosal ulcerations with an acute inflammatory exudate in the submucosa and muscularis.

Comment

The sudden shock cannot be explained on the basis of hemorrhage, because the total amount was under 500 c.c. Nor was there enough evidence of infection to explain the symptoms and findings on the basis of a generalized sepsis. It is also evident that the vascular thrombi formed as a result of the amniotic fluid, not prior to its entrance, because the amniotic fluid appears in the center of the thrombi. The liver and renal changes were not characteristic of eclampsia or pre-existing renal disease and there was no evidence of pre-existing heart or lung disease.

Thus, in my opinion, death was due to the pulmonary emboli of amniotic fluid. The patient survived the initial shock, but succumbed to the complications which arose from it. These were bilateral pulmonary infarcts, cardiac failure, and hepatorenal failure.

The entrance of the amniotic fluid into the maternal circulation in this case is not as clear-cut as in some reported cases. It is unfortunate that the placenta was not kept for careful pathologic examination. However, the fact that it was an abruptio placentae indicates that maternal blood sinuses were opened prematurely. Also the sanguineous character of the amniotic fluid indicates the probability of some communication between it and the endometrial cavity, no matter how small.

The case is interesting because of the following features:

1. It demonstrates either a delayed reaction to the emboli or two showers of pulmonary emboli. If there were two showers of emboli, which seems most likely, the latter ones were probably blood thrombi which resulted from the coagulant action of the fluid.
2. The patient was only 20 years of age, which is, I believe, the youngest age yet reported in such a case.
3. In this case the contractions were not severe, forceful, or tetanic.
4. The fetus was not exceptionally large or the pelvis inadequate.
5. The symptoms of chest pain, cough, bloody sputum, and râles were such that a diagnosis of pulmonary infarction could be made clinically and the appropriate treatment started.
6. The patient survived almost 31 hours after delivery, thus giving an opportunity to study the fate of the emboli at that stage.
7. The findings and observations of previous reports are confirmed.

Summary

A case of fatal pulmonary infarction due to emboli of amniotic fluid is presented and discussed. The unusual aspects of the case are enumerated.

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CYTOLOGICAL DETECTION OF UTERINE CANCER IN PRIVATE OBSTETRICAL AND GYNECOLOGICAL PRACTICE

Based on an Analysis of 104 Consecutive Positive and Suspicious Smears From 8,148 Private Patients

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THE value of cytological diagnosis of incipient cancer of the cervix is universally accepted. However, its practical value as a routine office procedure on every gynecological or obstetrical patient is still debatable. Most of the reports on large numbers of cases have come from clinics or cytological laboratories associated with medical schools or teaching centers. Major disadvantages listed by some of the clinics are: lack of trained personnel, excessive costs, lack of the specificity of the positive smear, and questionable advantages over the time-honored methods of history, inspection, palpation, and biopsy of all suspicious lesions.

The purpose of this study was to evaluate the reliability of the positive or suspicious smear report from a private laboratory and determine further the usefulness of the routine cervical smear in the detection of early malignancy and premalignant conditions in private practice.

This study is based on the analysis of the uterine malignancies and premalignant or borderline lesions detected in the first 104 consecutive positive or suspicious smears. Premalignant or borderline as well as malignant lesions are included in this study. The reasons for including premalignant or borderline lesions are: (1) that a few of these were actually questionable preinvasive cancer; (2) accumulating evidence indicates that some of these atypical anaplastic lesions may be precursors of noninvasive cancer; (3) premalignant lesions exfoliate well-differentiated anaplastic cells having characteristics of early or young malignant cells which are not infrequently indistinguishable from the cytology of early preinvasive cancer. Those cells having the cytological characteristics of well-differentiated early malignant cells are interpreted by us as suspicious or positive for a borderline or preinvasive malignancy, depending upon the quantity of these abnormal cells and the degree of anaplasia present.

On the other hand, we do not consider such atypical cellular disorders as basal-cell hyperplasia (Grade I or Grade II), squamous metaplasia, and mild to moderate dyskaryosis as premalignant at the present time, but they are classified as atypical lesions. Therefore, all positive or suspicious smears obtained from cervices manifesting such atypical lesions proved by adequate biopsies are considered as false positives.

*With the collaboration of the Gynob group of obstetricians and gynecologists: Drs. C. R. Kennedy, P. L. Martin, C. A. Isham, W. B. Henderson, R. L. Hoffman, G. S. Hardie, S. H. Smith, and T. A. Slate.

Methods and Material

The smears were obtained mostly as a routine measure in the private practices of 8 obstetricians and gynecologists. There were 8,148 new patients, and 8,551 smears, which include repeat smears within six months. Repeat patients after six months were considered as new patients. All smears from this group were sent to one private "gyne-cytological" laboratory from July, 1950, to June, 1952. A fee of $3.50 was charged by the laboratory to each patient for complete staining, reading, and report to the doctor. This covered all our costs for technician screening. No fee was charged by the collaborating gynecologists for obtaining the smear during a routine examination.

One smear was usually obtained from each patient by the Ayre[2] "surface biopsy" method with a wooden spatula or tongue blade. Care was taken to include cells from the squamocolumnar junction. Occasionally a second smear was taken at the same sitting if one was considered inadequate, but all smears taken from one patient at one sitting were recorded as one smear in our reports. These smears were immediately placed in equal parts of 95 per cent alcohol and ether and allowed to fix for 30 minutes or more.

At the beginning of our study both a cervical and a vaginal smear were taken from each patient. We gradually realized that the vaginal smear rarely added any more information than the cervical smear alone. Therefore, to simplify matters and lessen the work of the laboratory technician, the vaginal smear was abandoned as a routine procedure. We requested it only if the initial smear revealed atypical cylindrical cells, with the thought in mind that more information might be obtained if these cells were of fundal origin.

The smears were stained by the Papanicolaou method with some modifications. The screening was done by the cyto-technician. All highly atypical, suspicious, or positive smears were reviewed by the senior author before a final report was submitted.

Multiple biopsies, including the squamocolumnar junction, or "cold cones" were obtained from most patients with a Class III, IV, or V smear. A dilatation and curettage were also done when indicated by clinical symptoms or by the finding of anaplastic columnar cells. Each final microscopic report was made by a reliable pathologist. In this group over 95 per cent of the microscopic diagnoses were made or verified by the senior pathologist at Mercy Hospital,* the remainder by other qualified pathologists in the city.

Classification of Smears

We have followed a modification of Papanicolaou's classification which emphasizes detection of the earliest possible preinvasive or borderline lesion. The earliest detectable anaplastic cell with malignant characteristics places that smear in the suspicious or positive groups. In our cytological reports to clinicians we included a description of the type of abnormal cells and suggested further studies as follows:

1. Negative for malignant cells (not suspicious of cancer).
   a. Entirely negative. Repeat smear in 6 to 12 months, or
   b. Some benign abnormalities present. Repeat smear in 3 to 6 months.
2. Definitely atypical cells present (not suspicious of cancer).
   The type of abnormal cells is specified. Usually we suspect a benign atypical lesion or inflammatory change. Repeat smear in 3 months or biopsy as indicated by clinical findings.

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3. Highly atypical cells present.
   The type of abnormal cells is specified. We suspect a marked atypical lesion or possible premalignant lesion or preinvasive cancer. Advise immediate repeat smear and/or proper biopsies.
4. Suspicious.
   a. For borderline lesion or possible preinvasive cancer, or
   b. For possible endocervical or endometrial cancer, or
   c. For possible unclassified malignant cells.
5. Positive.
   a. For preinvasive cervical cancer, or
   b. For endocervical or endometrial cancer, or
   c. For unclassified or classified mature malignant cells.

Studies and Results

This study was undertaken by the Gynob group of gynecologists and obstetricians. Close collaboration was given to us by each member in carrying out this work. The gynecologist submitting the greatest number of routine smears was rewarded by a larger number of early malignancies detected.

Positive or Suspicious Smears.—Table I shows the results of a follow-up study of 104 consecutive positive or suspicious cervical smears as taken from 8,184 private patients.

TABLE I. ANALYSIS OF 104 CONSECUTIVE POSITIVE OR SUSPICIOUS SMEARS FROM 8,148 PRIVATE PATIENTS

NUMBER OF PATIENTS	DIAGNOSIS	CYTOLOGICAL INTERPRETATION
20	Invasive epidermoid cancer of cervix	1 suspicious 19 positive
48	Preinvasive cancer of cervix (one preinvasive adenocarcinoma)	4 suspicious 44 positive
14	Premalignant or borderline lesions of cervix	3 suspicious 11 positive
4	Adenocarcinoma of uterus (fundal)	4 positive
5	Cervices cauterized after Papanicolaou smear but before biopsy*	2 suspicious 3 positive
6	Insufficient follow-up for final diagnosis†	2 suspicious 4 positive
7	False positive or suspicious (exclusive of 14 premalignant or borderline lesions)	1 suspicious 6 positive

*These cervices early in the study presented such mild benign-appearing erosions that the gynecologist felt that cautery could safely be done before receiving cytological report. Follow-up smears and biopsies have been negative.

†Patients had inadequate biopsies before cauterization or transfer to Navy Hospital or physicians in other cities.

Invasive Epidermoid Carcinoma of the Cervix.—There were 20 patients with invasive epidermoid carcinoma of the cervix (Table II). Of this group, 3 presented benign-appearing lesions or a normal cervix. These were early invasive carcinomas and would have been missed had it not been for the positive smears. The remaining 17 were grossly suspicious enough to warrant biopsies. This indicates that a careful history and pelvic examination are sufficient in detecting most, but not all, cases of invasive carcinoma.

Repeat cervical smears taken experimentally from advanced lesions were consistently positive. The average ages and the clinical findings are listed in Table II.

TABLE II. ANALYSIS OF INVASIVE EPIDERMOID CARCINOMA OF CERVIX IN 8,148 PATIENTS

NUMBER OF PATIENTS	STAGE	AVERAGE AGE	APPEARANCE OF CERVIX			SMEAR	REMARKS
			NORMAL (GROSS)	BENIGN EROSIONS OR CERVICITIS (GROSS)	SUSPICIOUS LESION (GROSS)		
8	I	50.1	1	2	5	1 Susp. 7 Pos.	Three cases in this group showed only minimal invasion, 2 with benign-appearing lesions and 1 with normal-appearing cervix
4	II	44.7	0	0	4	4 Pos.	Several of these patients had repeated smears. All were positive
5	III	58.4	0	0	5	5 Pos.	Repeated smears for study from several Stage III and one of the Stage IV cases were positive
3	IV	53.3	0	0	3	3 Pos.	

Total, 20. Average age, Stages I and II, 47.4 years. Stages III and IV, 55.8 years. Papanicolaou smear valuable in detection of 3 cases. Remaining 17 cases suspected or clinically diagnosed.

Preinvasive Carcinoma.—Among 48 patients with microscopic noninvasive carcinoma of the cervix detected by the smear, 36 presented normal-appearing cervices as reported by their respective gynecologists; 7 presented benign-appearing erosions and cervicitis; 2 had innocent-looking leukoplakias of the cervix and only 3 had suspicious lesions (Table III). Invasion was ruled out in all cases by multiple sections of the biopsied tissues obtained by conization or hysterectomy.

The average age for the noninvasive carcinoma was 34.6 years, which is slightly below the ages as reported by other authors.[3, 8, 10]

Proportion of Cancers Undetectable Except by Smears.—Of the total preinvasive carcinomas encountered in our studies, 43 cases most likely would have gone unrecognized had it not been for routine cytological studies. These patients presented normal cervices or benign-appearing lesions (Table III). The remaining 5 cases we feel would have been biopsied and a carcinoma most likely discovered without cytological studies. These findings verify the initial impressions obtained by Martin, Slate, and Merritt[6] on the value of the routine smear in detection of incipient cervical cancer.

Conversely, as stated before, only 3 of all the invasive carcinomas would have been missed except for the positive smear.

Premalignant or Borderline Cervical Lesions.—There were 14 patients with premalignant or borderline cervical lesions (Table IV). Microscopically, all of these lesions showed definite disrupted epithelial pattern with anaplasia and

atypism sufficient to be considered premalignant or borderline, but not pronounced enough to be diagnosed by the pathologist as carcinomatous (Fig. 1). The average age of this group was 30.1 years. This age gradient together with the appearance of the cells suggests that this type of lesion may be the progenitor of preinvasive carcinoma.

TABLE III. PREINVASIVE CARCINOMA

NUMBER OF PATIENTS	AVERAGE AGE	SMEAR	APPEARANCE OF CERVIX				REMARKS
			NORMAL (GROSS)	BENIGN EROSIONS OR CERVICITIS (GROSS)	LEUKOPLAKIA (GROSS)	SUSPICIOUS (GROSS)	
48	34.6	4 susp. 44 pos.	36	7	2	3	Invasion was ruled out in all cases by multiple sections from biopsy material and/or conization from cervices. Extension into glands not considered invasion.

TABLE IV. PREMALIGNANT OR BORDERLINE LESIONS

NUMBER OF PATIENTS	AVERAGE AGE	SMEAR	APPEARANCE OF CERVIX				REMARKS
			NORMAL (GROSS)	BENIGN EROSIONS OR CERVICITIS (GROSS)	LEUKOPLAKIA (GROSS)	SUSPICIOUS (GROSS)	
14	30.1	3 susp. 11 pos.	7	3	1	3	Histological diagnosis based on definite intraepithelial anaplasia which is suggestive but not sufficient to warrant a diagnosis of cancer.

False Positives.—There were 7 positive or suspicious smears which did not seem to originate from a definite premalignant or malignant lesion after an apparently adequate diagnostic survey (Table V). After a review of the smears we interpreted 2 of them as atypical instead of positive in the light of our present knowledge. However, for strictly statistical purposes and in accord with other authors, 14 of the premalignant or borderline lesions should be added to these 7 cases, making a total of 21 false positives.

False Negatives.—As far as we know, there are only 3 cases (0.036 per cent) of false negative results consisting of one early epidermoid carcinoma and 2 cases of endometrial carcinoma. We realize that the percentage of false negative smears is difficult to evaluate accurately in this type of study. However, all clinically suspicious cervical lesions regardless of the smear findings were biopsied during this study. All patients having irregular uterine bleeding suggestive of carcinoma had a diagnostic dilatation and curettage.

Cervices With Positive Smears but Cauterized Before Histological Confirmation.—Early in this study, 5 patients with positive or suspicious smears

had the cervices cauterized at the same time the smear was taken. Thus any histological evidence of any possible small focus of preinvasive carcinoma or borderline lesion was destroyed. Follow-up smears thus far have been negative. This group is of interest in that the gynecologist felt so sure that each of these patients had benign cervicitis at the time of cauterization that a biopsy was not done.

Positive Smears With Insufficient Follow-up.—There were 6 patients with positive or suspicious smears who had insufficient follow-up for evaluation. Some were lost to the Navy Medical Department or other physicians while others had insufficient or inadequate biopsies before treatment was instituted in the form of cauterization or conization.

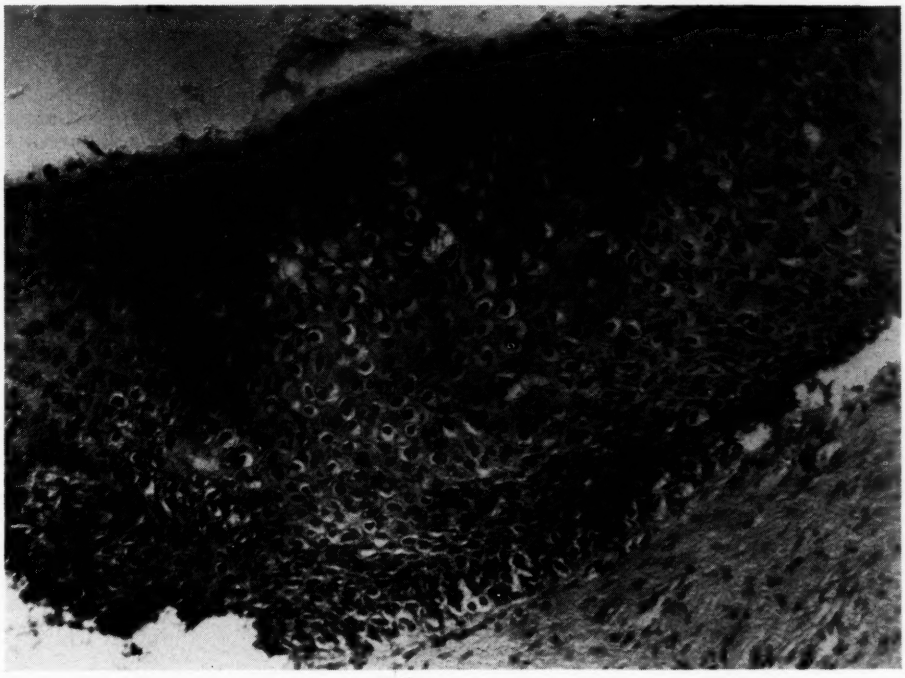

Fig. 1.—Premalignant lesion of cervix from patient aged 41 years. Note marked intraepithelial anaplasia but not sufficient to be diagnosed as carcinomatous.

Positive Smears With Indefinite or False Negative Initial Biopsies.—There were 9 patients with positive smears who had one or more negative or doubtful biopsies before a definite diagnosis of cancer of the cervix was made (Table VI). This suggests that one or several negative biopsies do not rule out an early cancer of the cervix. Multiple circumferential biopsies of the squamocolumnar junction or "cold cone" biopsies have given us the best diagnostic results following the positive or suspicious smear. Multiple or serial sections of the tissue submitted are advisable for the diagnosis of focal microscopic lesions and to rule out invasion.

Age Distribution and Carcinogenesis in Relation to Age.—Most of our preinvasive cancers were found in patients under 40 (Table VII). Seventeen (33.4

TABLE V. ANALYSIS OF FALSE POSITIVE SMEARS (SUSPICIOUS AND POSITIVE) (EXCLUSIVE OF PREMALIGNANT AND BORDERLINE LESIONS)

NAME	AGE	SMEAR	CLINICAL APPEARANCE	PATHOLOGICAL DIAGNOSIS	FOLLOW-UP
H. B.	51	Pos.	Normal	Chronic endocervicitis with metaplasia at squamocolumnar junction	Coned tissue revealed negative for cancer. Review of smear positive. Being followed
K. L.	39	Pos.	2 erosion bleeds easily	Chronic endocervicitis and endometrial hyperplasia, Grade II	Follow-up smears neg. Review of previous pos. smear interpreted as atypical columnar cells
L. W.	38	Susp.	Normal	Chronic cervicitis and endometrial hyperplasia	Laparotomy, rectosigmoid carcinoma with metastases to regional nodes. Review of smear—suspicious
S.	29	Pos.	Normal	Chronic cervicitis with epidermization and proliferative endometrium	Review of smear—atypical
H. M.		Susp.	2 cervicitis	Basal-cell hyperplasia. Chronic endocervicitis. Hyperkeratosis; squamous metaplasia	Follow-up smears neg. Cone and curettage neg. Review of smear—pos.
M. H.	38	Pos.	1 erosion	Chronic endocervicitis and basal-cell hyperplasia	Cone—no malignancy. Review of smear—pos. for early malignant squamous cells
E. T.	32	Pos.	Normal	Chronic endocervicitis with epidermization	Curettage, biopsies of cervix, and cone revealed no malignancy. Review of smear—suspicious

per cent) were patients between 20 and 30 years of age and an equal number were between 30 and 40 years of age. Ten (71.4 per cent) of our series of premalignant lesions were from patients under 35 years of age of whom 4 (21.4 per cent) were 19 years of age (Table VIII).

The average age of the premalignant group was 30.1 years, in comparison to 34.6 years of those with preinvasive carcinomas and 47.4 years of those with invasive carcinomas (Stages I and II). Table IX shows the relation of age to carcinogenesis and a comparison with other authors' findings.[3, 8, 10]

The average age of patients seems to increase in sequence with the stages of pathogenesis of carcinoma—borderline cancer to preinvasive to early invasive to advanced carcinoma. This is in accord with Nieburgs and Pund's[8] findings (Table IX).

Cytological Characteristics of Preinvasive Carcinoma.—In our study we were unable to distinguish cytologically between borderline lesions and early preinvasive carcinomas of the cervix (Fig. 2). But there appears to be a distinctive cytology associated with these early lesions. The most characteristic findings are well-defined, hyperchromatic, large nuclei with moderate to large amounts of cytoplasm. The increased or heavy chromatin particles are usually clearly visible. These changes may be seen in the superficial, intermediate,

or basal cells. The cells usually appear singly or in loose groups, rarely in large clumps (Fig. 3). There is usually an absence of free malignant nuclei. The bizarre cellular changes of invasive carcinoma are characteristically absent. These cellular characteristics have been reported by some previous workers[1, 7] but not accepted by others. However, the cytology associated with late preinvasive carcinoma shows more pronounced malignant characteristics and is often not unlike that of early or minimal invasive cancer (Fig. 4). By late preinvasive carcinoma we mean moderate to marked glandular invasion without invasion of the stroma (Fig. 5).

Fig. 2.

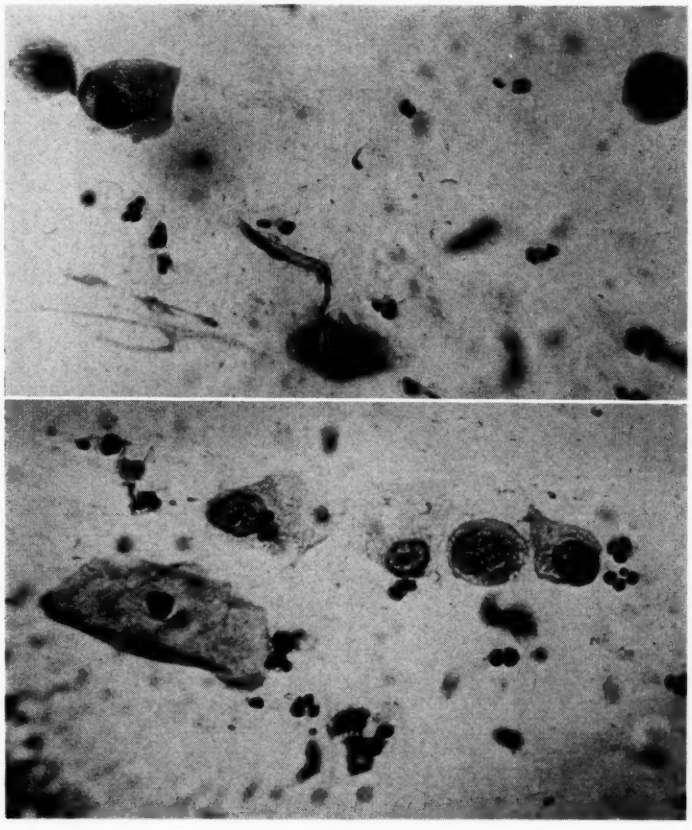

Fig. 3.

Fig. 2.—Anaplastic cells exfoliated by premalignant lesion of cervix. Note especially anaplastic basal cell on right side and similarity with cells in Fig. 3.

Fig. 3.—Anaplastic well-differentiated, intermediate and basal cells having early malignant characteristics exfoliated by early preinvasive carcinoma of cervix.

Although we were able to detect cytologically most of our preinvasive lesions, we do not mean to imply that we can always differentiate the invasive from the preinvasive carcinoma. However, in our studies, there appears to be a distinct parallelism between various grades of anaplastic cytological and histological changes. Further investigative studies are needed for better evaluation of this relationship.

TABLE VI. PATIENTS WITH POSITIVE SMEARS, BUT WITH ONE OR MORE INDEFINITE OR NEGATIVE BIOPSIES BEFORE FINAL DIAGNOSIS OF MALIGNANCY WAS CONFIRMED

NAME	INITIAL BIOPSY	FOLLOW-UP	FINAL DIAGNOSIS
P. D.	Preinvasive in one area not conclusive	Cold cone, biopsies—no malignancy. Serial sections of initial block—definite preinvasive	Preinvasive carcinoma
C. H.	6-4-51. Curettage. Large polyp, nonmalignant	Bleeding cont'd 8-2-51. Total hysterectomy—adenoma malignum	Adenocarcinoma of fundus, Grade I (adenoma malignum)
P. H.	5-20-51. Biopsies and curettage negative	Continued spotting 8-30-51. Total hysterectomy—intraepithelial adenocarcinoma of cervix	Intraepithelial adenocarcinoma of cervix
P. H.	Biopsies of anterior lip—negative	Multiple biopsies—carcinoma in situ	Carcinoma in situ
V. H.	Biopsies of anterior lip—potentially malignant dyskaryosis	Multiple biopsies—carcinoma in situ. Hysterectomy—carcinoma in situ	Carcinoma in situ
T. H.	12-5-51. Biopsies—chronic endocervicitis and basal-cell hyperplasia	1-5-52. Biopsies—preinvasive carcinoma	Carcinoma in situ
G. N.	6-25-50. Curettage, slight endometrial hyperplasia	3-23-51. Biopsy—intraepithelial carcinoma	Hysterectomy—preinvasive carcinoma
A. R.	Initial biopsies negative, 10-30-50	Biopsy—preinvasive carcinoma. Hysterectomy—preinvasive carcinoma	Preinvasive carcinoma
D. V.	12-26-50. Biopsies negative	11-1-51. Biopsies and hysterectomy—carcinoma in situ	Preinvasive carcinoma and leukoplakia

TABLE VII. AGE DISTRIBUTION IN PREINVASIVE CARCINOMA, 48 PATIENTS

	AGE IN YEARS					
	19-20	20-30	30-40	40-50	50-60	AVERAGE 34.6
Number of Patients	1	17	17	8	5	Total 48

TABLE VIII. AGE DISTRIBUTION IN PREMALIGNANT LESIONS, 14 PATIENTS

	AGE IN YEARS					
	19-20	20-30	30-40	40-50	50-60	AVERAGE 30.1
Number of Patients	4	3	4	3	0	Total 14

TABLE IX. CARCINOGENESIS IN RELATION TO AGE

	AVERAGE AGE	YOUNGEST	OLDEST	NIEBURGS AND PUND AVERAGE AGE	PUND AND AUERBACH AVERAGE AGE	CUYLER ET AL. AVERAGE AGE
Borderline	30.1	19	44	31	0	0
Preinvasive	34.6	19	59	40	36	37.6
Stage I and II carcinoma	47.4	37	62	Covert Ca. 46	42	48.3
Stage III and IV carcinoma	55.8	47	74	Overt Ca. 50	49	

Fig. 4.

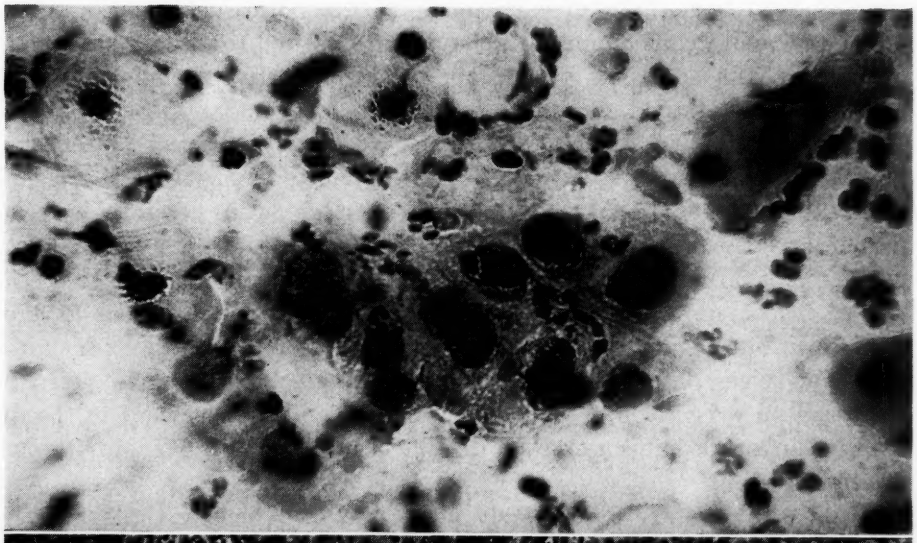

Fig. 5.

Fig. 4.—Groups of malignant squamous cells exfoliated by a late preinvasive carcinoma of cervix with moderate glandular involvement.

Fig. 5.—Late preinvasive carcinoma of the cervix. Note entire gland replaced by carcinoma on right half of photomicrograph. Multiple sections showed no invasion of stroma.

Comment

Carcinoma in situ of the cervix is generally accepted today as a definite histological entity. More evidence is gradually accumulated to suggest that this lesion may be the progenitor of clinical invasive epidermoid carcinoma,[4, 5]

just as some of the premalignant or borderline lesions may be the precursors or actually the progenitors of carcinoma in situ. More scientific studies on cellular morphology and abnormal behavior are needed to understand the true significance of the so-called premalignant or borderline lesions and of the slightly better-understood carcinoma in situ.

In spite of extensive cancer publicity we are still seeing patients with advanced carcinoma of the cervix. If we assume that most invasive cervical carcinomas are preceded by carcinoma in situ or even possibly by a premalignant or borderline lesion, then our diagnostic study should be directed toward these usually symptomless incipient lesions. The time-honored methods of history, inspection, palpation, and biopsies of all suspicious lesions have been inadequate in our hands in the diagnosis of early incipient lesions in normal-appearing cervices or in those having benign-appearing lesions. Our study has revealed an over-all increase of between 200 and 300 per cent in the diagnosis of preinvasive cancer and borderline lesions since we adopted routine smears in our practice.

In this study we are particularly interested in detecting the earliest possible incipient malignant lesion. We believe it is important to learn to recognize the cytological changes that indicate early preinvasive carcinoma or borderline lesions, so that a more careful search can be made for them. Such a need is shown in our study where 75 per cent of the preinvasive carcinomas and 50 per cent of the borderline lesions were from normal-appearing cervices.

The average age of 34.6 years for our patients with preinvasive carcinoma is slightly lower than that given in other reports as previously mentioned. This may be due to the fact that our study was based on routine screening of private patients regardless of age and clinical findings.

We are convinced that proper biopsies, including the squamocolumnar junction and endocervix or "cold cone" biopsies, are essential in the diagnosis of early incipient cervical lesions following a positive or suspicious smear. Single or multiple biopsies taken at random do not necessarily rule out an early lesion. Conversely, a negative cervical smear, although highly accurate, does not always rule out a malignancy. Every suspicious cervical lesion should be biopsied irrespective of a supposedly negative smear.

At present we are inclined to believe that the cervical smear, when properly evaluated and under control, is one of the most accurate tests available today for the early detection of cervical malignancies and premalignant lesions in private practice, and a reliable test to indicate the absence of carcinoma of the cervix when used in conjunction with a good pelvic examination. Various methods of surface biopsies can be used instead of the cervical smear, but these methods lack the simplicity and practicability for routine use in private practice.

Again one must reiterate that there are limitations. There must be cooperation between the cytologist, pathologist, and the physician using the routine smear. A positive smear does not necessarily mean that the patient has cancer. There are still false positives and false negatives. The final diagnosis must rest on histological confirmation.

Summary and Conclusions

1. One hundred four (1.27 per cent) positive or suspicious smears were obtained from 8,148 private patients. An investigation of these smears revealed 20 patients with invasive carcinoma of the cervix; 48 with preinvasive carcinoma of the cervix; 4 with fundal adenocarcinoma; and 14 with premalignant or borderline lesions. Five patients had cauterization of benign-appearing lesions before histological confirmation. There were 7 false positive results (exclusive of 14 premalignant or borderline lesions) and 6 patients had insufficient follow-up for final diagnosis.

2. Anaplastic cells appearing to have early malignant characteristics were interpreted by us as suspicious and positive in order to stimulate greater search for early preinvasive carcinoma and borderline lesions.

3. Approximately 75 to 89 per cent of our preinvasive carcinomas and 5 per cent of our invasive cancers would have been missed had it not been for the routine cervical smear.

4. Benign-appearing lesions and normal-appearing cervices may harbor early incipient carcinoma. Cautery of erosions should not be done unless cytological studies or biopsies are negative. Otherwise histological or cytological evidence of early malignancy may be eliminated.

5. The average age of patients seems to increase in relation to the pathogenesis of the stages of carcinoma—borderline carcinoma to preinvasive to early invasive to advanced carcinoma.

6. There appears to be a distinctive cytology associated with borderline lesions or early preinvasive carcinoma.

7. One or more biopsies taken at random do not rule out a preclinical carcinoma following a positive or suspicious smear. A "cold cone" biopsy or multiple circumferential biopsies of the cervix including the squamocolumnar junction and endocervix are essential for the diagnosis of early incipient lesions detected by the smear.

8. The routine cervical smear, if properly evaluated and under control, seems to be a practical and sensitive test for the detection of preclinical and early carcinoma of the cervix in a private gynecologic and obstetric practice.

9. Histological confirmation must be obtained before treatment is instituted and before a patient is led to suspect she has a malignancy.

Addendum

Since this study was undertaken we have screened by cervical smears an additional 4,312 private patients up to Dec. 1, 1952. From this group there were 12 positive smears, 18 suspicious, 13 highly atypical (Group III), from which were detected 9 premalignant or borderline lesions, 9 preinvasive carcinomas, 4 invasive carcinomas, 1 false positive, 1 false negative, 4 false highly atypical smears, and 16 were without follow-ups at present. We are continuing our study with the intent of reporting our further progress.

We are indebted to Dr. C. R. Kennedy for all our photomicrographs.

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Department of Case Reports
New Instruments, Etc.

ACUTE SODIUM DEFICIENCY IN A POSTPARTUM PRE-ECLAMPTIC PATIENT

Report of a Case

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ACUTE sodium deficiency in an adequately treated pre-eclamptic patient must be regarded as a rare complication. The clinical and laboratory data of the case here presented are unusually well documented, and it is believed that useful information can be obtained from a proper interpretation of these data. They cast considerable doubt upon the correctness of the original diagnosis of pre-eclampsia, if sodium or water retention is a sine qua non of this disease.

The patient was a 23-year-old white woman who registered in the antepartum clinic on Aug. 15, 1951. The last menstrual period started on May 27, 1951, and the expected date of confinement was therefore March 5, 1952. The serological test for syphilis was negative, the blood group was A, the Rh factor positive. An x-ray examination of the chest was unremarkable, and the past medical history was noncontributory. The patient had one previous pregnancy in 1950 and the following summary on the antepartum course, delivery, and postpartum follow-up was supplied from the University Hospital where the delivery was performed:

One year preceding her first pregnancy the patient weighed 85.2 kilograms and the blood pressure was recorded as 138/86 to 145/90 mm. Hg. During the early antepartum course the patient gained 6 kilograms and there was a progressive increase in the level of the patient's blood pressure which, at 39 weeks, reached 160/120 mm. Hg. At that time edema was noted and proteinuria to the extent of 1.2 Gm. for 24 hours was recorded. A primary cesarean section was performed at 39 weeks and a living 2,295 gram infant was delivered. The postpartum course was uneventful. Blood pressure readings at 6 weeks and 3 months were 145/100 and 135/100 mm. Hg, respectively.

When first seen in our antepartum clinic on Aug. 15, 1951, the patient's blood pressure was 156/100 mm. Hg., the urine was negative, and she weighed 93.2 kilograms. The hemoglobin was 14.5 Gm., the uric acid 2.4 mg. per cent, nonprotein nitrogen was 42 mg. per cent, and serum protein 6.17 per cent. In spite of a 1,200 calorie salt-poor diet, the patient had gained 10.5 kilograms at the thirty-sixth week, and a progressive elevation in blood pressure and an increase in proteinuria were noted. She complained of intermittent vomiting throughout her pregnancy but persistently refused hospitalization until Feb. 10, 1952, i.e., during the thirty-seventh week. On admission to the hospital

the blood pressure was 184/120 mm. Hg. There was one plus pretibial and ankle edema. She weighed 104 kilograms and during the first 24 hours she excreted 1.2 Gm. of protein. Her reflexes were within normal limits. Because of the stated admission diagnosis of "pre-eclampsia, severe," the patient was subjected to a series of laboratory studies which included the determination of serum electrolytes, the blood volume, a determination of sodium space and total body water in addition to the usual admission routine. In the considered opinion of the attending obstetrician in charge of the case, this represented an "obviously severe pre-eclampsia potentially subject to imminent convulsions, who must be treated fully," and immediate termination of the pregnancy by cesarean section was advised. Accordingly, this operation was performed on the following morning and the patient delivered of a 3,062 gram infant at 37 weeks of gestation. She withstood the procedure well, but because of vomiting and paralytic ileus a Miller-Abbott tube was inserted on the second postoperative day. The tube failed to progress beyond the pylorus and copious amounts of gastric fluid were drained during the succeeding three days. Supposedly adequate hydration was maintained by infusion of dextrose solutions, but sodium chloride was withheld because of the clinical diagnosis of pre-eclampsia, which implied an edematous state with sodium retention. Most of the laboratory data and the results relating to the changes in fluid compartments are reproduced graphically in Fig. 1. Soon after the application of gastric suction a progressive clinical picture of muscular weakness, excessive fatigue, mental apathy, confusion, nausea, and diplopia developed. In addition, the patient complained of muscular cramps but there was no evidence of spasm. With the exception of an excessive desire for "an ice cream soda" the patient showed no signs of thirst. On the fourth and fifth postoperative days the clinical picture was so confusing that neurologists and ophthalmologists were called in for consultation. The diffuse neurologic disturbance was interpreted as a sign of cerebral edema and further sodium withdrawal was advised. On the evening of the fifth postoperative day the sodium content of a 24 hour urine specimen had dropped to zero and a reversal of the red cell-plasma ratio had taken place. Thus, on the sixth postoperative day the correct interpretation was applied to the laboratory data and prompt sodium replacement was instituted. The patient received intravenous sodium chloride supplemented by oral, enteric-coated sodium chloride tablets. There was a prompt return of urinary sodium output and a corresponding rise in serum sodium to within normal levels within 24 hours. The carbon dioxide combining power began to rise slightly above the normal, expected level, only to return to within physiological limits on the following day. After the serum sodium levels were established within the normal range, a slight decline in serum potassium was thought to represent a temporary shift of cations and the intravenous fluids were, therefore, supplemented with Mudge solution (40 meq. KCl:100 meq. NaCl per liter). Although the investigators were aware of the fact that supplemental potassium administration was not essential, it nevertheless represented a certain safeguard in this rather unexpected situation, and careful control of serum potassium levels would prevent the creation of hyperpotassemia. Following the establishment of an entirely normal range of serum electrolytes and a reasonable distribution of fluid spaces the patient had an uneventful course and was discharged in good condition on the fifteenth postoperative day.

During the antepartum course this patient presented the clinical picture of rather severe pre-eclampsia as manifested by hypertension, albuminuria, and a weight gain of somewhat more than 10.5 kilograms. On admission to the hospital the patient's deuterium oxide space and the sodium space (proportional to but not identical with the extracellular space) were 45.4 L. and 22.7 L., respectively. Although these values are numerically high, expressed as percentage of body weight, they are below the normal, expected range. The deuterium oxide space represented 45.6 per cent of body weight and the sodium space 22.8 per cent. If the basic distribution of lean body mass, fat, and water, as suggested by Messinger and Steele,[1] is accepted, it must be concluded that the weight gain exhibited by this patient during her pregnancy represented an increase in

lean body mass and fat, rather than a water retention. Further, the sodium content expressed in milliequivalents per kilogram was considerably below the normal level, indicating that a sodium depletion had taken place during the antepartum period.

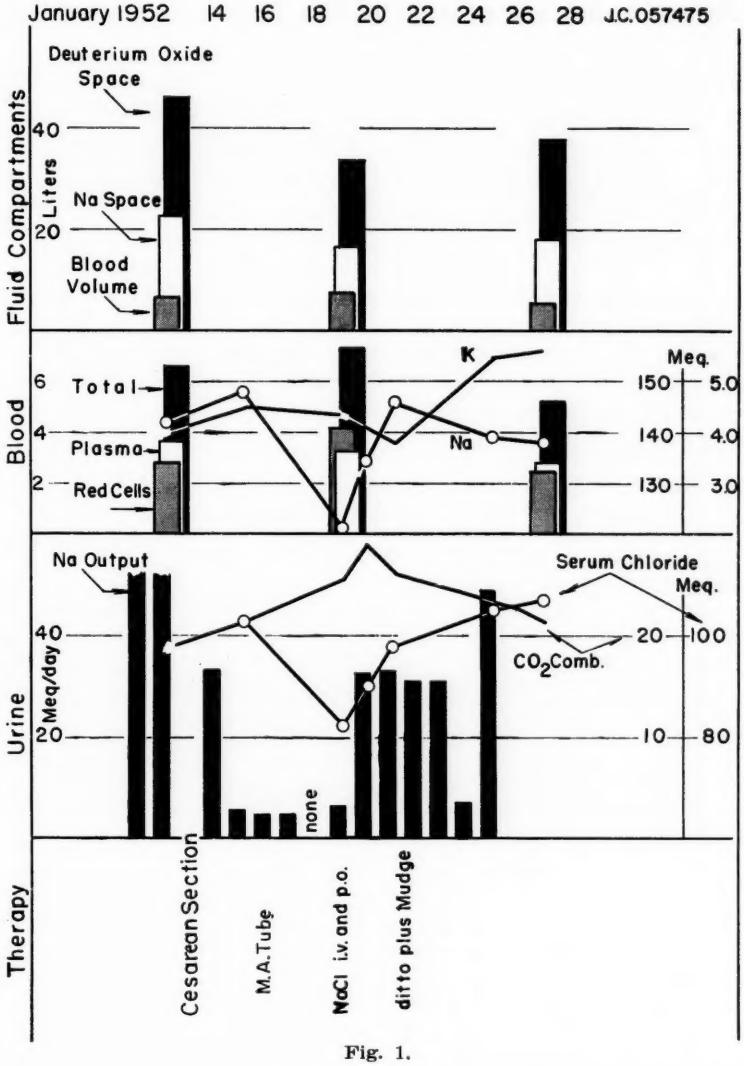

Fig. 1.

The progressive decrease in daily urinary sodium output during the immediate postoperative period should have been interpreted as a sign of further sodium depletion and the patient maintained on a positive rather than negative sodium balance. This fact, unfortunately, was not appreciated until the compensatory mechanisms for electrolyte and water conservation were completely exhausted. Based upon the figures mentioned above, there was a deficit of 480 meq. of sodium immediately following the operation. This deficit was aggravated by almost reckless removal of chloride ions (gastric juice) and it is not surprising that this depletion resulted in a rapid decline of the total sodium and chloride content of the body. The relatively more profound and more rapid removal of chloride ions explains the establishment of the classic picture of hypochloremic alkalosis. Associated with this profound metabolic imbalance there was a severe degree of dehydration as evidenced by a hematocrit of 58.8 per cent on the evening of the fifth postoperative day.

Severe pre-eclampsia or eclampsia without obvious edema has been considered as a particularly severe form of this disease. Eden's criteria as stated by Eastman[2] include the absence of edema as one of the signs which carries with it a grave prognosis, and older textbooks are said to consider "dry eclampsia" as its most severe form.[3]

The sequence of events would lead to the conclusion that this patient belonged in the group of "dry pre-eclamptics" whose treatment requires the most extensive laboratory assistance, without which the prognosis is likely to become grave. The signs and symptoms of electrolyte deficiency could easily be interpreted as manifestations of eclampsia and the downhill course accelerated by further withdrawal of electrolytes.

Summary

1. A case is presented in which an error in clinical diagnosis leading to acute sodium depletion could have been averted by proper attention to laboratory data.

2. A rapid and complete recovery was obtained after massive but careful replacement of sodium chloride.

3. The clinical picture of sodium deficiency may be strikingly similar to that of "severe pre-eclampsia," the correct diagnosis of which can be established only on laboratory data.

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LOW CERVICAL CESAREAN SECTION OF A TERM PREGNANCY IN UTERUS UNICORNIS UNICOLLIS ASSOCIATED WITH RENAL AGENESIS AND MALFORMATION OF THE BONY PELVIS

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THE occurrence of pregnancy in a uterus unicornis unicollis has been reported as occurring infrequently.[1] An associated renal agenesis however has been noted by other investigators and is probably not so infrequently encountered as current case reports would indicate.[2] Malformation of the bony pelvis has also been reported in association with uterus unicornis unicollis and renal agenesis in which instance a total hysterectomy was done for fibroid uterus.[2]

This reported case concerns a term pregnancy in a patient with all the above-mentioned anomalies and the delivery of a full-term living infant by low cervical cesarean section.

M. T., a 28-year-old primigravida, was first seen in our prenatal clinic on June 6, 1952. Her last menstrual period was Jan. 19, 1952, and her estimated date of confinement was calculated to be Oct. 26, 1952.

On the initial interview and examination she was found to be five months pregnant and several congenital anomalies were noted to be present. They were as follows: (1) marked left lumbar scoliosis, (2) atrophy of the left leg and thigh with limitation of motion of the left hip joint, (3) spina bifida occulta, (4) marked asymmetry of the pelvis, and (5) congenital absence of the left kidney.

There was a history of urinary incontinence since birth. At the age of 10 a laminectomy was done, followed three years later by a dorsal lumbar sympathectomy in an attempt to improve the urinary incontinence by producing a cord-type bladder. Since then the patient has required three to five self-catheterizations daily, and use of abdominal pressure with manipulation for bowel evacuation.

Following her initial visit to our clinic hospitalization was advised for x-ray studies and functional evaluation of the right and only kidney. The intravenous pyelogram (Fig. 1) taken on June 25, 1952, revealed a moderate right hydronephrosis with absence of kidney visualization on the left.

The bony pelvis exhibited an obliquely elliptical inlet with anterior rotation of the entire left side of the pelvis. There was also fusion of the left ilium and the fifth lumbar vertebra with a partially developed sacrum. This pelvic anomaly has been previously noted by other investigators.[3] The catheterized urine specimen on admission showed bacilluria and pyuria. Following hospital work-up she was discharged to the abnormal prenatal clinic on prophylactic terramycin for the bacilluria. On subsequent clinic visits the urine revealed a persistent bacilluria and pyuria without evidence of further kidney damage or systemic symptoms up until Sept. 2, 1952. Between Sept. 2, 1952, and Oct. 8, 1952, the patient had three admissions for acute flare-ups of pyelonephritis in spite of prophylactic antibiotic therapy as an outpatient.

Because of the bizarre pelvic deformity a low cervical cesarean section was done on Oct. 26, 1952, after thirty-eight weeks' gestation. A 6 pound, 7 ounce normal living female infant was delivered in good condition through a low transverse uterine incision followed by a Pomeroy-type tubal ligation. As anticipated, along with the agenesis of the left kidney and the anomalous pelvic development, a uterus unicornis unicollis with complete absence of the left tube and ovary was found.

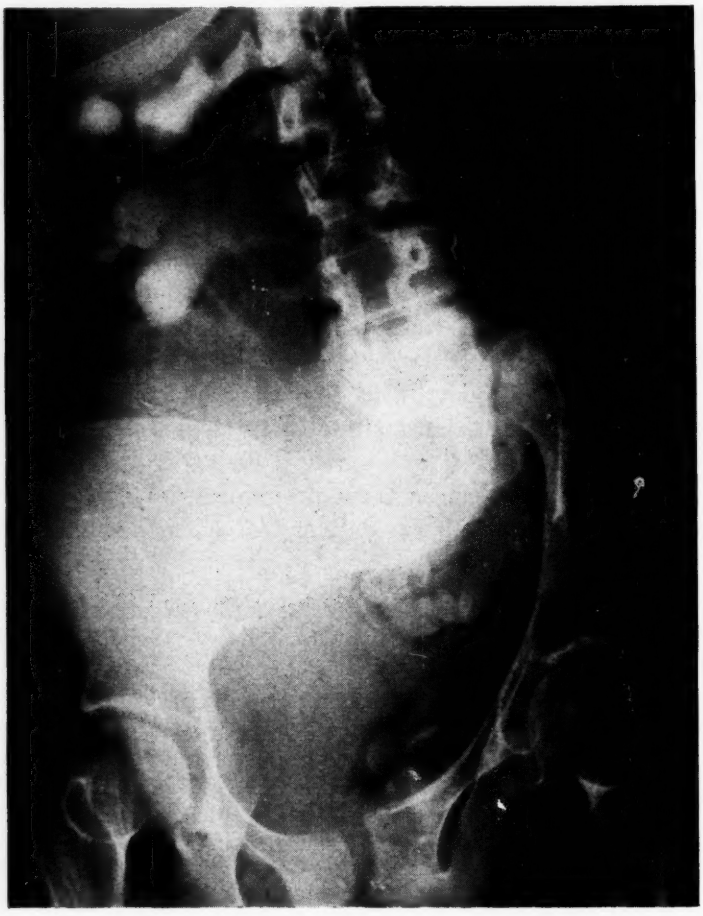

Fig. 1.—Urogram and bony pelvic anomaly demonstrating agenesis of left kidney.

In this case the congenitally absent left kidney and ureter followed failure in development of the left Wolffian duct. The absence of the left ovary and tube and the uterus unicornis represents failure in development of the left Müllerian duct system.

This case is reported in order to stress the frequency of associated anomalies of the female genitourinary system and to prompt further complete investigation of the other system when an anomaly of either is encountered.

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DYSGERMINOMA OF THE OVARY IN 17-YEAR-OLD NEGRO GIRL*

Case Report

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DYSGERMINOMAS are sufficiently uncommon that no gynecologist sees a large enough number to recognize them readily and to crystallize his ideas as to their management from personal experience.

It is therefore desirable when a case presents itself that the clinical behavior as well as the pathological factors be carefully studied and that the knowledge gained thereby be broadly disseminated, to the end that our collective knowledge regarding these tumors be developed as rapidly as possible.

This 17-year-old Negro girl entered the Cook County Hospital on Sept. 30, 1952, complaining of progressive abdominal enlargement and dyspnea of eight months' duration.

Past history was noncontributory. Past obstetrical history revealed that she had a normal spontaneous delivery one year prior to admission. Menstrual history was normal since birth of her baby.

Physical examination revealed a well-developed Negro woman with a protuberant abdomen, the size of a full-term pregnancy. The blood pressure was 110/80, pulse 100, respirations 22 and oral temperature 100° F. Examination of the lungs revealed absence of breath sounds on auscultation and dullness on percussion in the lower two-thirds of the right lung field. The left lung was clear.

X-ray of the chest revealed a marked right hydrothorax, the left was clear. Pelvic examination revealed a normal-sized uterus. The left adnexa were not palpable although no evidence of thickening or tenderness was present. The cavity of the uterus was probed to three inches, and the Clark test was negative. Speculum examination of the cervix revealed it to be long, hard, clean, with the external cervical os normal in appearance.

A thoracentesis was subsequently done and 2,000 c.c. of amber-colored fluid was obtained from the right chest cavity. This was centrifuged and found to be negative for cells and acid-fast organisms.

In an effort to determine the nature of the abdominal fluid a paracentesis was performed below the umbilicus in the midline. A bloody watery fluid was obtained which was centrifuged and yielded cells with deep-staining nuclei of uneven size which were reported to be malignant. Subsequent paracentesis in the left lower epigastric region yielded a clear straw-colored fluid. Unfortunately this specimen was not examined.

Laboratory findings were as follows: Hemoglobin 82 per cent, white blood count 4,750, Kahn test negative; urine negative for albumin and sugar; nonprotein nitrogen 26 and total protein 7.7 Gm. per cent.

On Oct. 18, 1952, the abdomen was entered with some difficulty since the omentum was interposed between a large tumor mass and the peritoneum of the anterior abdominal wall and was adherent to both. The omentum was separated from the mass which was

*Presented before the Chicago Gynecological Society, Feb. 20, 1953.

identified as the right ovary. The small bowel was closely adherent to this large cyst and was carefully separated. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. Her postoperative course was uneventful.

Further therapy consisted of a single injection of radioactive gold into the peritoneal cavity, dosage 65 mc. of Au^{198}. This was followed by a course of external x-ray therapy totaling 3,330 r skin dose single port posteriorly in lumbar regions 3, 4, and 5.

X-ray of the chest on the sixth postoperative day revealed an absence of pleural fluid in both lung fields.

Pelvic examination two months after surgery was essentially negative except for questionable soft adhesions in the right flank region.

Pathologic Examination.—The specimen consisted of a uterus with cervix, left tube, and ovary attached. The left ovary was of normal size and contained numerous cysts measuring up to 8 mm. which were filled with purulent material. A corpus luteum was also present. The tube was normal. The other ovary was converted into a basketball-sized soft mass. The outer surface was smooth and traversed by numerous blood vessels of various caliber. The tube was attached to this large mass. The consistency was soft. On cut section the surface was made up of numerous varying-sized cystic compartments measuring from 2 to 40 mm. in diameter. In some areas they were filled with clear bloody fluid and in others with necrotic material. Microscopic section of the tumor of the ovary revealed much necrotic tissue showing degenerated cells with large deep-staining nuclei. In places where the blood supply was sufficient the tumor tissue revealed many cells with large deep-staining nuclei and vacuolated cytoplasm. These resembled spermatogonia. In addition there were smaller cells of lymphoid appearance with scanty cytoplasm. The latter resembled spermatids. Pathological diagnosis: Dysgerminoma.

It may seem to some that we were radical in removing the uterus and opposite ovary. This procedure was based on the fact that one-third of these tumors recur after removal. Döderlein has reported that extrapelvic metastases occurred in 13 out of 50 cases (25 per cent), and that 10 of these 53 patients died, 18.8 per cent. For the present we shall continue to regard all of these tumors as malignant which in our clinic calls for a panhysterectomy and removal of adnexa the same as for all malignant tumors of the ovary. The duration of the tumor in the abdomen before the patient entered the hospital and its clinical behavior during these eight months increased our apprehension that it might have spread to the peritoneum. Novak feels that a radical removal should be undertaken in all cases in which the tumor seems to have extended beyond the ovary. The adherent bowel and omentum made this problematical.

As far as we know, this is the first time radioactive gold has been used in the peritoneal cavity in this type of case. We used it for what it might be worth and are observing the results in our follow-up examinations. To date there have been no untoward symptoms from its use and there is also no clinical evidence of recurrence of the malignant growth. There was no recurrence of the symptoms that would indicate further accumulation of fluid in the chest.

FOREIGN BODY IN THE VAGINA FOR TWENTY YEARS

Report of a Case

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A FOREIGN body as the cause of vaginal discharge in children is fairly rare. This condition is frequently considered by pediatricians and gynecologists; however, occasionally there may be circumstances in which this condition is overlooked. Schauffler,[1] in 1942, stated that he had treated 267 small patients for vaginal discharge and removed five foreign bodies from the vagina. He found safety pins in 3 instances, a red wax crayon in the fourth, and twigs and splinters in the fifth.

The following case is presented in which a foreign body was in the vagina for 20 years.

Report of a Case

The patient was a 23-year-old nulligravida, who complained of almost continuous, profuse, foul vaginal discharge and intermittent lower abdominal and pelvic pain. The patient's mother stated that she first noticed a foul vaginal discharge at about 3 or 4 years of age which necessitated frequent changing of her clothing. The child had been seen by many physicians and had received repeated treatments over the years.

A tonsillectomy and appendectomy were performed in 1939. There was no history of a gynecologic investigation being done at that time. In 1942 the patient was 13 years of age and a recorded examination showed the vagina to be only 1 inch in depth. The impression was a congenital abnormality of the upper third of the vagina with no evidence of patency between the uterus and vagina. An operation was performed which consisted of dilatation and drainage and exploration of the upper vagina. There was some foul-smelling fluid in the posterior portion of the upper vagina and also dense fibrous bands across the vagina in this area.

From 1942 until 1948 the symptoms were approximately the same. The vaginal discharge persisted and there was some pain with the menstrual periods. Periodic examinations apparently showed the vagina to be shortened as previously described. In 1948 the patient married and there was an episode of 2½ months' amenorrhea in 1950. Examination showed induration in the left parametrial region. Later she requested help because of failure to conceive, but infertility studies were not carried out.

Physical examination on Jan. 18, 1952, showed a well-developed, well-nourished, attractive young white woman, who weighed 93 pounds. Her general development was good and there were normal secondary female sex characteristics. The abdomen was negative except for an appendix scar which was firm. Pelvic examination showed normal external genitals. The introitus easily admitted a finger to a depth of 5 cm. There was a small opening at the apex of the vagina from which there came a purulent discharge. On rectovaginal examination the cervix was felt 3 cm. superior to the apex of the vagina. The uterus was anterior and appeared to be normal in size, shape, and consistency. There were induration, fixation, and tenderness in the paravaginal areas.

On May 1, 1952, a uterosalpingogram was attempted. The film showed that there was no dye in the uterine cavity, but a metallic foreign body was shown lying in the pelvis to the left of the midline about the level of the ischial spines. It appeared to measure approximately 8 mm. in diameter and slightly over 2 cm. in length.

On May 28, 1952, a uterosalpingogram done under anesthesia (Fig. 1) showed the uterus to be well filled with the dye, but the tubes were not patent. In the left paravaginal area there was a cavity containing the previously described metallic tube. At the time of this procedure a vaginoplasty was done to enlarge the upper portion of the vagina.

Fig. 1.—Metallic cylinder in abscess cavity to left of vagina.

Old records were carefully reviewed to determine whether or not some plastic procedure had been attempted previously in which a metallic tube had been placed in the upper vagina. There was no evidence that this procedure had been done. Follow-up examinations showed the upper vagina to be increased in diameter and the metallic foreign body could be touched with a probe.

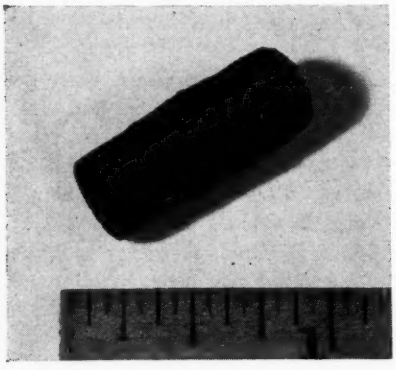

Fig. 2.—Encrusted foreign body which is apparently a metal cap to a lead pencil.

On Oct. 6, 1952, under Pentothal anesthesia, the foreign body was removed after exposure by colpotomy. It was found to be a small metallic cylinder which measured 2.2 cm. by 7 mm. (Fig. 2). One end was open and it was encrusted with rust. It lay in an abscess cavity in which there were foul-smelling, greenish-yellow pus and a small amount of gas.

Follow-up examinations showed less induration in the left paravaginal area and no tenderness. There was a small amount of granulation tissue in the upper vagina on the left.

Comment

The metallic foreign body seemed to be the metal top to a lead pencil. It was thought that this object was lost in the vagina when the patient was 3 years old and its presence caused a severe vaginitis with ulceration of vaginal mucosa and subsequent lodging of the foreign body in the left paracolpium. Then followed the chronic inflammatory reaction over the years and cicatrization of the fibrous tissue about the upper portion of the vagina until it was completely obliterated.

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INTRAPARTUM HEMORRHAGE FROM THE CEREBRAL VESSELS OF AN ANENCEPHALIC FETUS

A Case Report

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INTRAPARTUM hemorrhage may be placental, maternal, or fetal in origin. Hemorrhage from the placenta may be due to low implantation, separation of a normally implanted placenta,[1] rupture of a marginal sinus[2] (which constitutes one-third of all cases of placental bleeding), and hemorrhage from vasa previa.[2, 3] Maternal hemorrhage may be due to rupture of genital varicosities[3] (rare), rupture of the uterus, or laceration or erosion into a blood vessel of the cervix. Hematuria,[4] bleeding from hemorrhoids or urethral polyp[4] may be mistaken for uterine bleeding.[5]

Fig. 1.—Anencephalic fetus, with brain surface unprotected and sharp bony edges projecting.

Fetal origin of intrapartum hemorrhage is somewhat rare. Reference to hemorrhage from the cerebral blood vessels of an anencephalic fetus could not be found in the literature. In view of the absence of any protection of the friable choroid plexus, the rarity of such bleeding is surprising.

Case History

Mrs. G., a 24-year-old primigravida, estimated as due to deliver on November 10, was sent to the Cedars of Lebanon Hospital on December 4 at noon.

The membranes had ruptured two hours previously and she had mild uterine contractions and moderate to profuse bright bleeding with some clots. The fundus, measured with a pelvimeter, was 28 cm. above the pubes. The blood pressure was 136/94. Presentation and position were left occipitoanterior and the fetal heart rate, in the left lower quadrant, was 158 per minute at 1:30 P.M. Rectal examination was difficult for the presenting part was high and the cervix soft and compressible. A diagnosis of central placenta previa was made.

Mild labor continued with moderate bleeding. Despite the bleeding, the patient's pulse and general condition remained good. Two hours after admission, the fetal heart sounds had become faint and had slowed from 158 to 96 per minute. The mother was then prepared for immediate operation and oxygen was administered.

A low cervical cesarean section was done and a normally situated placenta was found. A stillborn female anencephalic baby was delivered (Fig. 1). The soft presenting part which had been palpated rectally proved to be the exposed brain substance of the fetus, and was apparently the source of the bleeding. The fact that the bleeding was from the fetus through the blood vessels of the exposed brain, may explain the presence of the normal blood pressure and good condition of the mother.

Autopsy Findings.—The placenta and cord presented no significant pathology. The entire calvarium of the fetus (including bilateral frontal, parietal, and occipital bones) was absent and there was a soft necrotic mass of purplish-red and gray brain tissue projecting from the top of the skull. No other external abnormalities were noted. Microscopic examination of the nervous system showed a lack of the normal architectural pattern. The cortex was thin, poorly convoluted, and with cellular immaturity throughout. The blood vessels were dilated and congested. There were focal hemorrhages into the brain parenchyma and accumulations of hemosiderophages suggestive of old hemorrhage.

Summary

A case is presented of intrapartum hemorrhage at term. A soft, compressible mass at the cervix was incorrectly diagnosed as placenta previa. Hemorrhage was from the cerebral blood vessels of an anencephalic fetus.

Roentgenography of the lower uterine segment might have been of much help in diagnosing this condition. Correct diagnosis is important in this type of case because there is danger that the sharp bones of the malformed skull may cause serious laceration of the bladder and other maternal tissues unless careful precautions are taken.

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THE EFFECTIVENESS OF THE CERVICAL CAP AS A CONTRACEPTIVE METHOD

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ALTHOUGH widely used in Europe,[1-5] the cervical cap has found only limited acceptance by the medical profession of this country.[6-11] Reasons for this reluctance on the part of American physicians are mainly confusion of the cervical cap with harmful intracervical or intrauterine devices and lack of a statistical evaluation of its effectiveness. To provide the information hitherto lacking, we have compiled a series of cases from our private practice (H. L. and H. G. L.) in New York City. We are grateful to the late Dr. R. L. Dickinson who encouraged us to write this paper and contributed the illustrations.

In most instances, we consider the cervical cap preferable to the vaginal diaphragm for psychological reasons, since it can be left in situ for a number of days up to the full length of the intermenstruum. It is a great comfort for many women to feel fully protected at all hours throughout each cycle, without the need for technical preparations at each occasion of intercourse. We have had a surprisingly large number of patients who opposed the diaphragm because the idea of having to insert it prior to intercourse takes away the spontaneity of the act and destroys its romantic mood. Many of these patients find it equally obnoxious to prepare themselves every evening for possible cohabitation by routine insertion of the diaphragm.

We, therefore, tend to prescribe the cervical cap for all patients in need of protection against pregnancy unless (a) the patient on her own initiative requests a diaphragm, or (b) contraindications to the use of the cap are found on examination.

The cap is contraindicated in the presence of deep cervical lacerations extending to the vaginal vault, cervical erosions or Nabothian cysts, extreme shortness or extreme elongation of the cervix. Other contraindications are acute and subacute inflammatory conditions of the adnexa. Rarely, a malodorous secretion collects inside the cap after it has been worn for a number of days in succession; but this condition can be remedied by adding a chlorophyll preparation to the contraceptive cream. There are cases also where the husband feels the presence of the cap during intercourse. Some women who cannot learn self-insertion and self-removal of the cap object to the necessity of one or two monthly visits to their doctor for replacement of the contraceptive. Some, with irregular menstruation, may find that the flow has started before they had a chance to have the cap removed.

On the other hand, we prescribe the cap for women who cannot use the diaphragm for anatomical or functional reasons, such as a short anterior vaginal wall, a cystocele, a lacerated or relaxed pelvic floor, third-degree retroversion or acute anteflexion of the uterus, or allergy to rubber which, though rarely, may be present in either wife or husband. While the diaphragm cannot be used for virgins, we have seen a number of patients with intact hymens who in the course of premarital consultation could be fitted with a small cervical cap, without pain or injury.

We now use plastic caps made in the United States, but some of our older patients are still wearing their caps of European manufacture. In each case we have attempted to make our patients realize that no mechanical device, however tightly fitted, can completely prevent the tiny spermatozoa from slipping through and that the most important function of the cervical cap (as well as of the diaphragm) is to keep the external os in close contact with the chemical contraceptive.

The cap prescribed by us is made of a clear plastic material, Lucite, in the shape of a truncated cone, with a narrow smooth-edged rim. Because of its form the cap is self-adjusting. The swelling of the cervix during the cycle makes the cap descend slightly and a decrease in

the diameter or length of the cervix makes it ascend. The rim of the cap adheres snugly to the vaginal fornices, but its dome should not be in contact with the external os. The cap attaches itself firmly to the mucous membrane; any attempt to dislodge it increases the partial vacuum between the cap's dome and the cervix. If menstruation sets in unexpectedly while the cap is in place the flow escapes easily. The rim of the cap facilitates self-insertion and removal. While some discoloration of the plastic material may occur after prolonged use the same cap can be used for several years.

With the exception of a few extreme cases we have found three sizes satisfactory: "large" (36 mm. diameter), "medium" (30 mm.), "small" (24 mm.). Instruments for measuring the cervical circumference or special fitting caps are superfluous. The size of the cap can easily be determined by rough estimation. Sufficient space should be allowed between cervical os and cap. Too tight a fit is not desirable.

Before insertion, the cap is cleansed with water and soap, but never boiled. It is then half filled with spermicidal jelly or cream. The patient is placed in the lithotomy position, two fingers of one hand separate the labia. The cervical cap is held between index and middle fingers of the other hand and inserted into the vagina, following the posterior wall to the posterior fornix. Here the cap is released and will slip almost automatically over the cervix.

Fig. 1.

For self-insertion the patient is first taught to feel her own cervix. Then she herself is to follow the same technique as described above. Self-insertion in standing posture is facilitated if the patient will put one foot on a chair while the knee of the other leg is slightly bent. For removal of the cap, index and middle fingers are inserted into the vagina, reaching high up in the fornix. As the rim of the cap is reached it is tilted away from the cervix. The cap is grasped between the two fingers and removed. The tilting movement is important; this maneuver, by permitting the entry of air into the cap, relieves the suction and thereby allows easy removal of the cap. Even after having been in place for three weeks it is usually found still half-filled with the jelly or cream.

A total of 143 case histories are available for statistical analysis (C. T.). This represents all histories in the files except records of patients who were instructed in the use of the cervical cap, learned self-insertion immediately, and were not heard from again. An effort was made to follow up all patients, but the conditions of private practice made it impossible to achieve perfection in this respect.

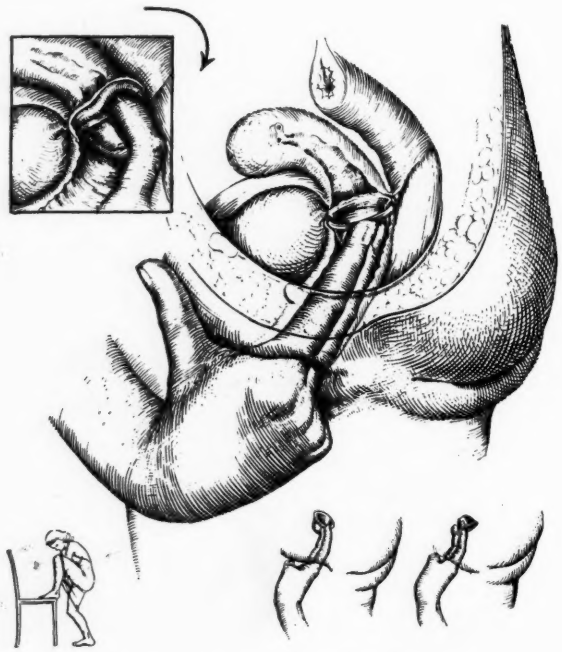
Lack of complete follow-up has introduced a bias into our data but the bias increases, rather than reduces the apparent pregnancy rate and therefore does not invalidate our findings. The material comprises four groups of patients:

Group A, Patients who visited the doctor regularly every month for removal and/or reinsertion of the cap,

Group B, Patients who remained under his care for reasons other than their need for protection against pregnancy,

Group C, Patients who had ceased to attend the office but were located and interviewed, and

Group D, Those who returned from time to time for checkup of the cap or because they had become pregnant while using it.



Self-removal of cervical cap

Fig. 2.

These categories are not sharply separated and a patient may move from one class to another. The histories of the patients of Group A are, by definition, complete and there is no reason to assume that Groups B and C are anything but representative of the generality of cap users who practice self-insertion. Class D could introduce a distortion if those women who returned to the physician were either more or less successful in the use of the cap than women who did not return. The fact that a parallel series of diaphragm-and-jelly users from our practice yielded the comparatively high rate of 13.7 pregnancies per 100 years of exposure (based on 44 accidental conceptions in 320 woman-years) indicates that the bias in our data on the cervical cap likewise operates in the direction of increasing the apparent pregnancy rate.

Of the 143 patients known to have used the cap for one month or longer, 101 were still users at the time the records were abstracted. The remaining 42 had given it up for one reason or another (Table I). The three patients who discontinued because of an erosion should not have been fitted with a cap. In one case only, the erosion and adnexal disease had apparently grown worse during 3 months' use of the cap, while in two instances the erosion remained stationary. One of these two concerned a newly wed woman for whom the cap was prescribed as a temporary measure prior to cauterization (1 month). The other patient with a small erosion tolerated the cap for 15 months. In one case the cap apparently produced a discharge which ceased upon removal. Of the two "poor fits," one involved a woman with an infantile uterus and an elongated cervix; in the other case, the cervix was too short. Both patients used the cap for one month only.

TABLE I. REASONS FOR DISCONTINUING USE OF CERVICAL CAP

Erosion	3
Discharge	1
Poor fit	2
Discomfort to wife	2
Discomfort to husband	2
Could not learn self-insertion	6
Feels unsafe	3
Accidental pregnancy	5
Wanted to become pregnant	6
Separation of couple	4
Hysterectomy	3
Menopause	1
Cap broke	1
Not recorded	3
Total	42

As shown in Table II, the duration of exposure to the risk of pregnancy while using the cap ranged in individual cases from 1 month to more than 20 years. The aggregate exposure amounted to 4,415 woman-months or 368 woman-years. Not less than 92.4 per cent of this total was contributed by the 72 patients observed for more than a full year of exposure.

TABLE II. NUMBER OF USERS AND AGGREGATE EXPOSURE BY MONTHS OF OBSERVATION

MONTHS OF OBSERVATION	NUMBER OF USERS	AGGREGATE EXPOSURE (MONTHS)
1- 6	50	136
7-12	21	201
13-24	21	389
25-36	16	509
37-60	14	622
Over 60	21	2,558
Total	143	4,415

The number of unplanned pregnancies which occurred during the period of observation was 28 corresponding to a rate of 7.6 pregnancies per 100 years of exposure. This rate is not significantly different from the rates obtained by the most successful users of the diaphragm-and-jelly[12] and of condoms.[13, 14] It should be noted that this rate is based on all pregnancies without exception which occurred prior to a definite abandonment of the method. Since it is impracticable to classify users and exposure months by regularity and perfection of technique, any exclusion of pregnancies on similar grounds would result in misleadingly low rates. Among the 28 unplanned pregnancies there were 6 cases apparently related to the omission of a chemical contraceptive in the cap or otherwise faulty technique and 10 instances of admittedly irregular use or temporary interruption. In at least three cases in the latter

group the history suggested strongly the presence of a more or less unconscious desire for a baby (or another baby) on the part of the woman—against her own and her husband's well-considered judgment. For 12 pregnancies no explanation was recorded.

Insertion by the physician comprised a little more than two-fifths of the aggregate exposure with the cervical cap. The pregnancy rate during this time was not significantly lower than during exposure with self-insertion, suggesting a high degree of success in instructing the patients. It is our impression that the great majority of patients are eventually able to learn self-insertion of the cervical cap, but because our series does not include any cases followed for less than a month it is not possible to compute the exact percentage nor the average time required by them for mastering the technique.

It has been demonstrated[15] that when couples discontinue contraceptive measures in order to have a baby, at least one couple in four and perhaps as many as three in ten are able to achieve pregnancy within one month after the abandonment of birth control. At that time, the chance of conception is between 0.25 and 0.30 per lunar month. Thereafter it declines rather rapidly. The explanation for this is that couples differ greatly in their ability to achieve pregnancy. Those women who conceive most easily do so during the first few months after birth control has been given up. As time progresses the relatively fecund couples have eliminated themselves from the group and only the less fecund and sterile remain. A group of couples practicing contraception successfully is not subjected to this selective process and retains its high reproductive potential represented by a chance of conception of 0.25 to 0.30 per month. A pregnancy rate of 7.6 per 100 years of exposure, as computed for our cervical cap users, corresponds to a rate of about 0.005 per lunar month. Since 0.005 is 2 per cent of 0.25 and an even smaller fraction of 0.30, it can readily be seen that the likelihood of conception has been reduced by at least 98 per cent.

It has been pointed out that our material is apparently biased in the direction of an increased rate of accidental pregnancies. In addition, a number of our patients admitted omission of the prescribed cap on one or more occasions and/or faulty technique. We may, therefore, conclude that the physiological effectiveness of the cervical cap, under ideal conditions of use, must exceed 98 per cent. This high level of protection makes the cap a valuable addition to the armamentarium of the physician who has to advise his patients on the subject of birth control.

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AN INSTRUMENT FOR THE SIMS-HUHNER TEST

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A NEW instrument for performing the Sims-Huhner test has been devised. It has been noted that it is often difficult to get a good specimen of cervical mucus with a loop, a suction tube, or a smooth forceps. Difficulty is experienced because of the sometimes tenacious quality of the cervical mucus and because of the danger of contamination from lower in the cervical canal.

The instrument is made by modifying the common uterine packing forceps. It is most desirable that this instrument be of stainless steel, so that it will not chip. The end of the instrument is ground down for a distance of about 5 mm. Small cups, made to conform to the end of the blades and to approximate each other accurately, are welded in place (Fig. 1). The cups have a volume capacity of approximately 0.1 c.c.

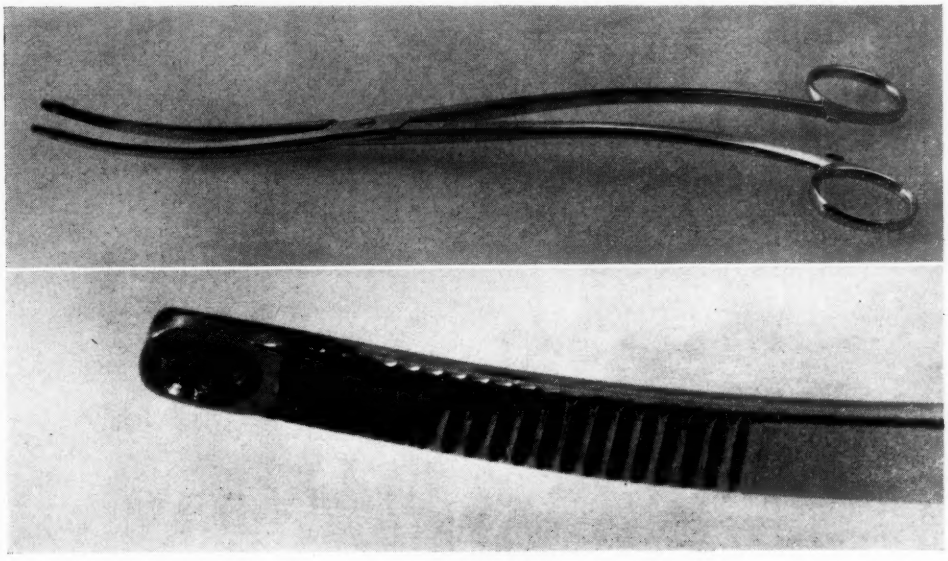

Fig. 1.

The instrument is introduced into the cervical canal closed. It is opened at the desired level, introduced slightly deeper, then rotated slightly and closed. The instrument is then removed and wiped off so that there will be no contamination from below. The specimen from the cups is quite adequate for study of the presence of spermatozoa.

The instrument has been used with gratifying results in my office and at the Infertility Clinic of the Department of Obstetrics and Gynecology of the University of California.

A MODIFICATION OF THE BIVALVE VAGINAL SPECULUM

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THE most popular vaginal speculum in use today is the Graves speculum. This is a bivalve instrument with Sims blades and two screw attachments to permit expansion which was first described in 1878.

This instrument is quite satisfactory when the patient is on a gynecological table with the legs flexed sufficiently to permit placement of the buttocks at the table edge. It is, however, always difficult, and at times impossible, to insert the instrument into the vagina with the patient in bed or if the legs are not sufficiently flexed, owing to the extension of the handle of the speculum into the surface of the bed or table.

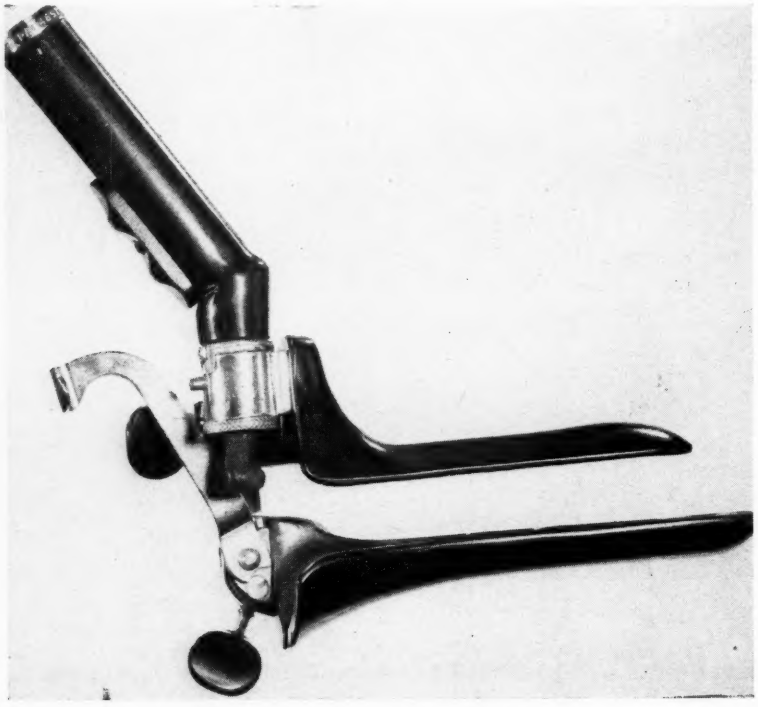

Fig. 1.—The modified bivalve vaginal speculum.

To overcome this difficulty I devised the instrument shown in the accompanying illustration which differs in only one respect from the Graves speculum. The handle of the modified speculum is attached to the short anterior blade whereas in the ordinary speculum

the handle is attached to the long posterior blade. The instruments are otherwise similar in ease of introduction, adequacy of exposure and mechanics of expansion, and self-retaining features. Following insertion, the handle of the modified speculum points away from the table surface toward the symphysis and thus avoids the objections described above.

This modified instrument is not intended to replace the ordinary bivalve speculum. It seems to have distinct advantages in the following instances: (1) for the examination of patients in the home; (2) for the examination of the hospitalized patient too sick to move to an examining table; (3) in patients with vaginal spasm who are unable to extend the legs laterally; and (4) in older patients with arthritis and with bony deformities who cannot be properly placed on gynecological examining tables.

AN APPARATUS FOR MAINTAINING THE ANESTHETIZED PATIENT IN THE KNEE-CHEST POSITION

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(From the Department of Gynecology of The Johns Hopkins University)

BECAUSE of the progressive increase in the number of culdoscopic examinations that are being carried out in this clinic, there is a great need for an apparatus to maintain the anesthetized patient satisfactorily in the knee-chest position. Through experience we have found that an anesthetized patient maintained manually in this position presents the following difficulties:

1. Because so much of the patient's weight is on the chest, there is marked angulation of the neck which results in poor respiratory exchange, and difficulty with anesthesia is marked.
2. It is difficult to maintain the patient in a constant satisfactory position.
3. Two assistants are required throughout the entire procedure.

A satisfactory apparatus has to satisfy the following requirements:

1. It must have sufficient strength.
2. It must be light enough to be easily applied to the operating table.
3. It must be capable of supporting the patient without exerting pressure on the abdomen or interfering with the blood supply to the legs.
4. It should not obstruct the operator or hinder the anesthetist.

We think the apparatus about to be described fulfills these requirements.

The supporting frame is made of ½ inch galvanized iron pipe and is fitted to the operating table by means of ⅝ inch iron rods bolted to the frame. These rods fit into the same fixtures which are used for supporting standard leg holders. The crank, crank shaft, buttock bar, and abdominal yoke are made of ⅜ inch galvanized iron pipe. The hooks on the buttock bar are ⅜ inch iron rods. The pulleys are 1⅜ inch, sheathed, marine type. The rope is ¼ inch cloth-bound bronze cable (marine steering cable). The abdominal yoke is so designed that no pressure is exerted on the patient's abdomen. When air is introduced into the abdomen the intestines fall cephalad and empty the pelvis. Galvanized chains are bolted to the ends of the yoke. By means of these one is able to correct for variation in patient size. The yoke is placed under the patient in such a manner as to bring pressure to bear on the iliac bones, inferior to the anterior superior iliac spines. The portions of the yokes which come into contact with the patient are adequately padded.

The approximate cost of the material used was $25.00. The simplicity of construction can best be borne out by the fact that all parts were prepared by a hardware store and we simply assembled them.

The patient is anesthetized in the dorsal recumbent position and a nasopharyngeal airway is inserted. She is then placed in the lithotomy position where a vaginal and perineal cleanup is carried out. The vulva is covered with a sterile towel, the patient turned to the prone position and the yoke put in place. The frame is then applied to the table, the chains attached to the yoke, and the patient elevated into the knee-chest position. The mechanical advantage is such that this requires little effort. The patient's

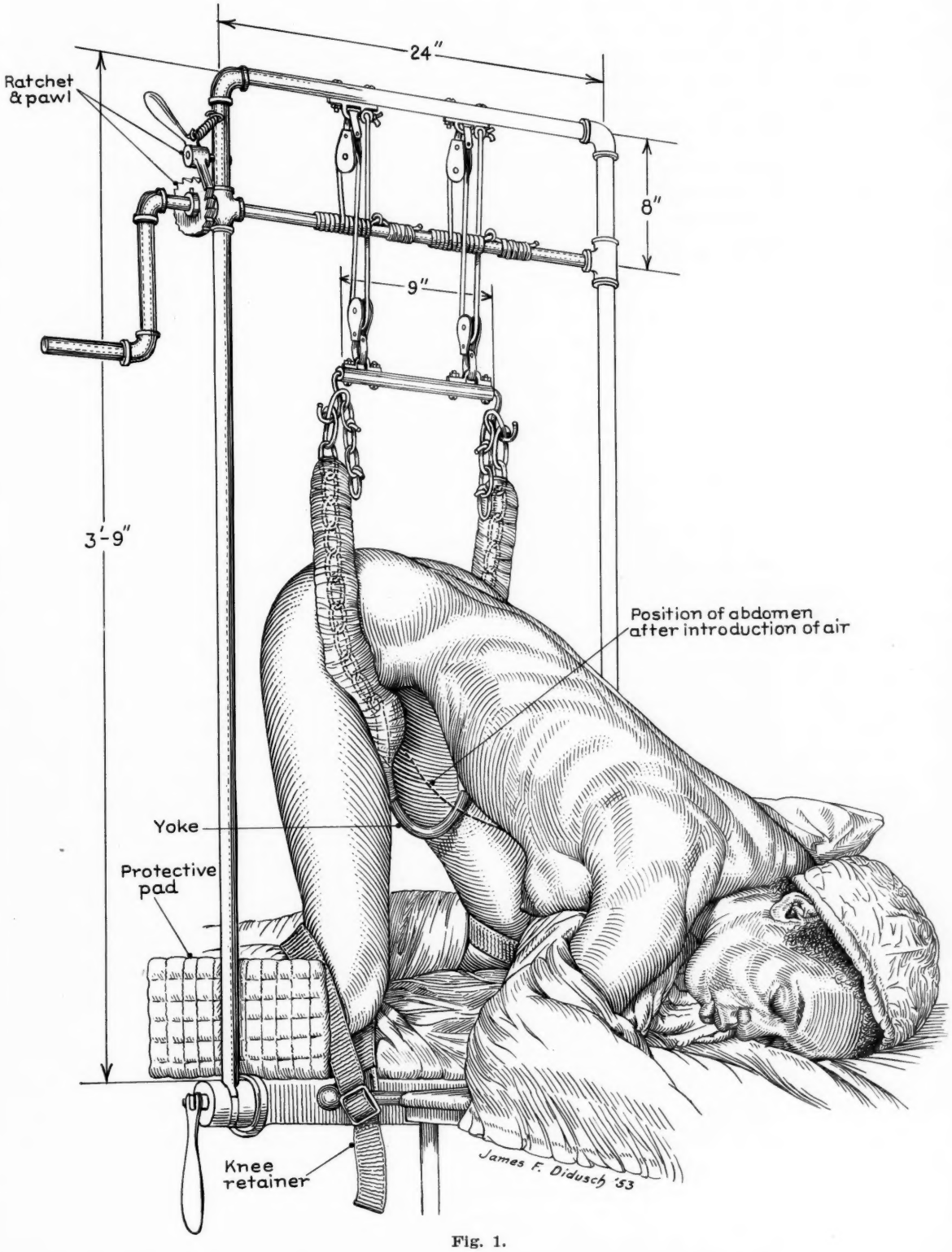
24"
Ratchet & pawl
8"
9"
3'-9"
Position of abdomen after introduction of air
Yoke
Protective pad
Knee retainer
James F. Didusch '53

Fig. 1.

knees are permitted to rest lightly on the operating table and are steadied by strapping them loosely to the sides of the table. The perineal nerve is protected by a pad between the knee and the frame. In the resulting position the patient's chest does not rest on the table and by insertion of a pillow to elevate the chest further a straight airway is maintained. The buttocks overhang the end of the table and a perineal drape is applied after removal of the perineal towel.

Although this apparatus was designed for culdoscopy it can be used for almost any procedure which is carried out on the anesthetized patient in the knee-chest position. An example of this would be the occasional vesicovaginal fistula which is repaired most advantageously in the knee-chest position.

Editorial

Foreign Contributions

WITHIN the last few months several articles from contributors from abroad have begun to appear in the pages of the JOURNAL. This represents a carefully considered although moderate change in editorial policy. This slight change in point of view nevertheless seems to deserve a word of comment.

The primary responsibility of the JOURNAL is certainly toward its American contributors, to the societies of the United States and Canada for which it acts as an official organ, and to the specialists of North America in obstetrics and gynecology who read the JOURNAL.

Yet we believe that the occasional appearance in our pages of a contribution from abroad will do much to add color and indeed breadth to the JOURNAL. Even a medical group as large as our own may fall into provincial habits in its scientific thinking and restrict itself to particular techniques or to the development of particular areas of interest, somewhat oblivious of the advances that are being made in other lands and appearing in other languages. Special tendencies of medical education and practice may give special opportunities to observe disease and its therapy peculiar to a given country. In the last generation we have, for example, come to give special significance to the statistics on cancer of the cervix from countries where the treatment of this disease has been largely centralized. On the other hand, diseases such as genital tuberculosis, chorionepithelioma, anemias of pregnancy, and conditions due to malnutrition are vastly more common and therefore more studied in certain countries abroad than here at home. These examples are offered with the final and obvious point that the inspiration for medical advance has no geographic limitations.

With these thoughts in mind the Editors are prepared to find space for contributions from abroad which may describe phenomena of health or disease relatively beyond our experience as well as those which, by a difference in scientific approach, promise to shed a different light on problems even well known to us.

The acceptance of an article from abroad imposes certain difficulties on contributors, Editors, and perhaps upon the readers. The contributor and his institution, their past work and reputation, may be relatively unknown in America. Our literary style, standards in illustrations, tabulations, and bibliographic systems are likely to be unfamiliar to the writer from abroad. The idiom of a foreign language, particularly the permissible colloquialisms of a medical journal, are difficult and the foreign flavor may persist even after an article has been subjected to a reasonable degree of editing. When this is evident it will at least attest the authenticity of the imported product.

There will, then, in the future appear from time to time in the AMERICAN JOURNAL articles from abroad. There is no intent to solicit these, nor to be more lenient in the editorial criticism to which they will be subjected. It is, however, our belief that medical advances are not to be circumscribed by language or nationality and that when material is sent to us that promises to be of value or of interest to our readers it should be accepted regardless of its source. This, at least, is our present view.

Howard C. Taylor, Jr.
William J. Dieckmann

Department of Reviews and Abstracts

CONDUCTED BY GEORGE W. KOSMAK, M.D., NEW YORK

Review of New Books

EDITED BY LOUIS M. HELLMAN, M.D., BROOKLYN, N. Y.

Anurie bei Chromoproteinurie. By Prof. Dr. Hans U. Zollinger, from the Pathologic-Anatomic Institute of the University of Zurich, Switzerland. 138 pages with 42 illustrations. Stuttgart, 1952, Georg Thieme Verlag. $3.50.

The author of this work has studied 55 cases of renal damage. All showed hemoglobin casts in the renal tubules. The causes of this condition are divided into ten groups.

A thorough discussion of the clinical course, pathologic findings, and physiologic alterations which occurred in these patients is given. The work closes with a discussion of the pathogenesis of the syndrome and some remarks as to therapy.

The author found the kidneys to be edematous. The glomeruli were avascular, with thickening of the basement membrane. The signs of tubular damage were demonstrable, beginning on the fourth day after the original renal insult. The principal tubular damage occurred in the proximal portion of Henle's loop. The proximal convoluted tubules showed flattening of the epithelial lining. The collecting tubules showed epithelial proliferation. In the distal portions of Henle's loop, tubulovenous aneurysms were formed. Characteristic pathologic lesions were not demonstrated in other organs, although there was a tendency to central necrosis of the liver lobules.

The author believes that shock and anoxia, the toxic action of hemo- or myoglobin, and the effect of protein-split products, singly or in combination, all play a role in the development of the syndrome. Decapsulation of the kidney has been as successful as any other means of therapy.

An excellent bibliography terminates the book. This is a thorough and provocative study of a difficult problem.

BRUCE A. HARRIS, JR.

Roentgenuroskopie. By Dr. med. habil. G. W. Gunther, Mannheim, Germany. 46 pages with 86 illustrations. Stuttgart, 1952, Georg Thieme Verlag. DM 13.50.

This short volume covers the subject of roentgenological urography. The renal pelvis, ureter, bladder, and urethra have been extensively studied and copiously illustrated with numerous excellent photographs.

BRUCE A. HARRIS, JR.

Die Zusammenarbein des Geburtshelfers, des Kinderartztes und des Serologen bei der Prophylaxe und Therapie der Neugeborenen-Erythroblastose. By Prof. Dr. P. Dahr, Prof. Dr. K. Schäfer, and Dr. A. Stadtmuller, Gottingen and Hamburg, Germany. 64 pages with 10 illustrations. Stuttgart, 1953, Georg Thieme Verlag. DM 5.70.

This book constitutes an elementary survey of the difficult and complicated subject of erythroblastosis. A brief outline of the history of the subject is given, followed by some elementary remarks as to its hereditary aspects. Diagnostic criteria, laboratory tests, methods of prophylaxis, and illustrative case histories are presented.

The volume is intended to serve as a brief and practical review of the subject, and in this it is successful. In some aspects, however, it is a trifle too elementary. For example, no mention is made of the Hr factors. Moreover, Rh is treated as if it were only one agglutinogen, instead of a whole group thereof. On the whole, however, the book is admirably adapted to its purpose.

BRUCE A. HARRIS, JR.

Clinical Obstetrics. By Clifford B. Lull, M.D., and Robert A. Kimbrough, M.D. 732 pages with 392 illustrations and 8 color plates. Philadelphia, 1953, J. B. Lippincott Company. $10.00.

This volume by twenty coauthors, most of them past or present members of the staff of the Pennsylvania Hospital, was originally undertaken under the editorship of the late Clifford B. Lull and has been brought to completion by Robert A. Kimbrough.

The book is divided into nine sections. An interesting foreword deals with the history of the Pennsylvania Hospital which is one of the oldest in the country. The first section deals adequately with the essential points of anatomy, physiology, and embryology, along with a chapter on fertility. Section two, which deals with antenatal care and normal pregnancy, contains an excellent chapter on nutrition and nutritional deficiencies in pregnancy which is based on a five-year study by the Nutritional Research Clinic. In the successive sections, the chapter on obstetric roentgenology is very good. The section on the newborn stresses breast feeding and includes an excellent chapter on the newer concepts of hemolytic disease of the newborn. An unusual chapter on the legal aspects of the practice of obstetrics is a welcome and valuable innovation. Obstetric analgesia and anesthesia are dealt with very fully with emphasis on various forms of regional nerve block. Continuous caudal analgesia, spinal, and saddle block anesthesia are described in detail. Paravertebral anesthesia is mentioned but not described. In the chapter on hemorrhages of pregnancy the use of oxytocin by the intravenous drip method is not mentioned in the treatment of premature separation of the placenta or postpartum hemorrhage due to inertia although many clinics have found this simple procedure of value.

The section on operative obstetrics is somewhat disappointing since only forty-five pages are devoted to this important aspect of the subject, while twenty-five pages are given to an elementary and repetitive outline of obstetric nursing practices. It is somewhat surprising to learn that the Kielland forceps "is rapidly falling into disrepute." The statement that "the aftercoming head in breech presentations demands the Piper forceps" is open to question. Mentum posterior is listed as a contraindication to forceps. Many operators use the Kielland forceps in the absence of disproportion.

The book contains no bibliographies in the strict sense but a list of references is appended to each chapter. The volume is of handy size and well printed. The illustrations are numerous and well chosen. The drawing of incomplete duplication of the uterus in F. 43 will doubtless be corrected in a subsequent printing. *Clinical Obstetrics* is a valuable addition to our obstetric literature and should prove useful to all who practice and teach the subject.

CLAUDE HEATON.

Problems of Infancy and Childhood. By Milton Senn, M.D., Sterling Professor Pediatrics, Yale University. New York, 1953, Joseph Macy, Jr., Foundation. 160 pages. $2.50.

This book is a transcript of a panel discussion on which were represented members of various disciplines: psychiatry, psychoanalysis, pediatrics, obstetrics, psychology, experimental physiology, sociology, etc. The discussion was based on three papers by Sibylle Escalona, Katherine M. Wolf, and Ann Stewart. These papers all showed the use of a new methodology in the study of infants' reactions during the first year of life. These papers demonstrate the usefulness of this methodology in revealing important new understanding

of the infants' emotionality, behavior, and physiological responses. Although this book is directed primarily to those interested in child development, its scope of interest includes all medical specialties.

This method studies infantile behavior in a framework of the child-mother continuum; the interactions between the mother and child; and some of the external familial and social factors bearing on this relationship. This enables the observers to gain a much more subjectively meaningful and dynamic understanding of the total infantile development, unlike Gesell's approach which gave a mass of objective data based mainly upon a rather static maturational development of the child. It presents a method of testing the reconstructed generalized hypotheses resulting from psychoanalytic research of older children and adults, through this direct observational method. It is noteworthy that under this close scrutiny such generalizations as "rejecting mother," "overprotective mother," etc., break down into partial functions of the actual child-mother interaction.

The obstetrician will be most interested in the study of the prenatal mother. These observations show that the pregnant woman's emotional orientation toward herself and the fetus may later influence her adaptation as a mother and influence the emotional and physical development of her child. It is important to note that in some mothers a supportive role taken by the obstetrician and/or other members of the obstetrical team can relieve tensions and anxieties sufficiently to prevent such symptoms as excessive childhood crying ("colic"). All physicians will be interested in how a tense mother can affect the physiological components of a child's behavior, such as swelling nasal mucosa, increased gastrointestinal motility, and heightened vasomotor response. These findings may indicate that a disturbed early mother-child relationship creates a proneness to later "psychosomatic" illness. However, the specific nature of the disturbances and proof of the validity of this deduction must wait further longitudinal study of the life of the child. The methodology used by these investigators is being extended for such studies.

All the panel participants emphasized the acute sensitivity of the infant to the mother's emotional reaction, transmitted at first directly through touch and smell, later by hearing and vision. The specific ways in which this contagion of feeling is transmitted to the child make fascinating and dramatic reading.

STANLEY R. LESSER.

Books Received

TITLE	AUTHOR	PUBLISHER
Adventures in Artificial Respiration	Peter V. Karpovich	Association Press, New York
Conduction Anesthesia	George P. Pitkin	J. B. Lippincott Co., Philadelphia
Die Geburtshilflichen Operationen	Heinrich Martius	Georg Thieme Verlag, Stuttgart
Die Verstandene Frau	Eberhard Schaetzing	J. F. Lehmanns Verlag, Munchen
Doctor in the House	Richard Gordon	Harcourt, Brace & Co., New York
A Guide to Obstetrics in General Practice	William C. W. Nixon and Eric B. Hickson	Staples Press, Inc., New York
A Modern Practice of Obstetrics	D. M. Stern and C. W. F. Burnett	Bailliere, Tindall & Cox, London
Morris' Human Anatomy	Ed. J. P. Schaeffer	The Blakiston Co., New York
Operative Gynecology	Richard W. Te Linde	J. B. Lippincott Co., Philadelphia
Roentgen, Radium and Radioisotope Therapy	A. J. Delario	Lea & Febiger, Philadelphia
Sexual Harmony in Marriage	Oliver M. Butterfield	Emerson Books, Inc., New York

Selected Abstracts

EDITED BY GEORGE W. KOSMAK, M.D., NEW YORK, N. Y.

Anesthesia, Analgesia

Pender, John W.: Rh Factor and the Anesthesiologist, Anesthesiology **13:** 608, 1952.

The purpose of this paper is to review and clarify the clinical implications of the Rh factor in order that the average anesthesiologist may have a clearer understanding of this very important subject. In 1940 Landsteiner and Weiner, while preparing anti-M sera in rabbits, discovered a new antibody. Rabbits' serum that had been previously immunized by the injection of blood from the rhesus monkey agglutinated 86 per cent of the erythrocytes in 45 samples of human blood. Thus the Rh factor was discovered. Those persons whose red blood cells were agglutinated by this serum were called "Rh positive" and those whose cells were not agglutinated were called "Rh negative," the designation "Rh" having been derived from the first two letters of rhesus monkey whose blood was first used for immunization of rabbit serum. In 1941 Levine and associates showed that in cases of hemolytic disease of the newborn the blood of all the fathers and their babies was Rh positive while 93 per cent of the blood of the mothers was Rh negative, thus establishing the Rh as an etiological factor in hemolytic disease of the newborn infant. This also pointed to the existence of subgroups of the Rh factor. The problem now seemed simple, viz., administer Rh-positive blood to Rh-positive recipients and Rh-negative blood to Rh-negative recipients. But this is not always so simple because of the difficulty in determining who is wholly Rh positive or negative. The Rh factor is a very complex substance and occurs in many types and combinations. At the present time there are six known anti-Rh sera. They are, according to Weiner, Rh_o, Rh_I, Rh_{II}, Hr_I, Hr_o, and Hr_{II}. According to Fisher's terms there are Rh D, C, E, c, d, and e. The nomenclature of Weiner is used in the United States and that of Fisher in England. Rh_o (D) is the most common subtype and accounts for 95 per cent of the dangers due to the Rh factor. The remaining subtypes are less dangerous but are not to be entirely ignored. Almost every person has a combination of three or more of these six subtypes of Rh in the blood cells. The question of heredity of the Rh factor is still not settled.

The incidence of isoimmunization and the development of the Rh antibodies following transfusion with Rh-incompatible blood is variable. It depends upon (1) the potency of the antigen; (2) the development of antibodies by the recipient; (3) the frequency of transfusion; and (4) the amount of blood transfused. Rh incompatibility occurs more frequently and is more serious in women than in men because women may be sensitized by pregnancy as well as by transfusion. Furthermore, the intramuscular injection of incompatible blood can produce Rh sensitization in the recipient. Modern methods of Rh typing are approaching the ideal. Experts, using all six anti-Rh sera, can accurately determine the Rh type and subtypes. Reactions of any consequence are rare. Prenatal determinations are likewise excellent; however, in the latter case, management in the Rh-negative group in the presence of Rh-positive husbands is not so successful. If hemolytic disease of the newborn is suspected for any reason, an antiglobulin test should be done on the baby's blood immediately or, in severe cases, an exchange blood transfusion is preferable.

In summary the author states that (1) every individual possesses one or more types of the Rh factor in his red blood cells; (2) the Rh types are determined by tests with six anti-Rh sera; (3) Rh typing is more difficult if the person has been transfused at any time with blood of a different Rh type; (4) certain types of blood must be considered Rh positive when used as donor blood and Rh negative when belonging to a recipient; and (5) there are two forms of anti-Rh antibodies, the complete and the incomplete. The incomplete form passes through the placenta to the fetal circulation more readily and thus produces hemolytic disease of the newborn. HARRY B. MATTHEWS.

O'Brien, Donough, and Roberts, Hilda: Endotracheal Insufflation With Oxygen in the Treatment of Asphyxia Neonatorum, Brit. M. J. **2:** 963, 1952.

The primary need in asphyxia neonatorum is oxygen, while of secondary importance is the method by which it is given so long as it is efficient. The long-term results of treating 66 severely asphyxiated newborn infants with oxygen administered by endotracheal tube are reported, while the difficulties encountered in trying to assess a single method are recalled. The infants included in the report had been aspirated, an airway inserted, and the infants placed in an oxygen rocker. If, after six minutes, there was no response under direct vision the pharynx was aspirated, an endotracheal tube inserted, and oxygen supplied intermittently at 20 cm. water pressure. As soon as respirations began, the tube was withdrawn. The period of treatment varied from 3 to 40 minutes, but was usually about 7.

Of the 66 newborn infants thus treated, 14 died. Five of these deaths would have occurred no matter what the therapy. Of the remaining 9 fatal cases, 7 infants responded but succumbed in from 5 hours to 4 days with atelectasis and evidence of amniotic fluid aspiration.

The 52 infants that survived had uneventful recoveries, except 2 who showed transient signs of cerebral irritation during the first 10 days of life. The deliveries had occurred during 1949 to 1951, and a long-term follow-up was carried out to evaluate possible permanent central nervous system damage. Of the 52 infants, 6 could not be traced and 3 were below 3 months of age. The remaining 43 infants were all examined clinically and appeared to be normal in every way. The authors feel that their intervention undoubtedly saved the lives of a number of infants and that recovery was uncomplicated by any permanent cerebral damage. They conclude that in experienced hands this method of resuscitation is safe, quick, simple, and efficient. JOHN T. COLE.

Cancer, Malignancies

Cross, Raymond G., O'Conner, M. Harris, and Holland, Peter D. J.: Placental Metastasis of a Breast Carcinoma, J. Obst. & Gynaec. Brit. Emp. **58:** 810, 1951.

A housewife, aged 35 years, married one year, mother of one child, was found to have a swelling in the right breast in November, 1949. This tumefaction was removed and pathological examination revealed malignancy. Radical mastectomy was immediately performed. Pathological examination of the removed breast showed no malignancy. Presumably all malignancy had been removed with the original biopsy specimen. Early in 1950, when she was 18 weeks pregnant, examination revealed nothing suspicious of metastatic malignancy. However, 3 months later, when she was 30 weeks pregnant, enlarged supraclavicular glands were observed. Deep x-ray therapy was given, the pregnant abdomen being screened with protective layers of a lead apron. Very severe pain in the sacroiliac region and in the right mandible required heavy sedation. Because the patient was steadily losing ground, induction of labor at 36 weeks of pregnancy was performed and a 5 pound healthy child was spontaneously delivered. The puerperium was uneventful. X-ray therapy was continued but the patient died a few months later. No autopsy was permitted but the uterus was found to be free of malignancy. Pathological examina-

tion of the placenta revealed areas of malignancy of the same general type found in the primary breast cancer. The authors call attention to the fact that "metastases" is probably not the correct term when the tumor "is reproduced in another individual." They suggest that "placental transplant" would be a better term. An excellent photomicrograph and a brief résumé of the literature on placental metastases by Sir Eardley Holland (1949) conclude the report. HARRY B. MATTHEWS.

Wimhöfer, H.: The Treatment of Carcinoma of the Cervix; Ten-Year Review of Cases at the Heidelberg Clinic, Geburtsh. u. Frauenh. **12**: 317, 1952.

The treatment of carcinoma of the cervix at the Heidelberg Hospital was reviewed for the years 1936 to 1945. In the general picture, where all stages of carcinoma were treated, an over-all 5 year cure rate of 44 per cent was noted. Therapy instituted consisted of (1) surgery alone, (2) preoperative radiation followed by surgery, and (3) radiation alone utilizing both x-rays and radium implantation. In reviewing the results, the author feels that preoperative radiation followed by radical surgery gives the best results where no or minimal gland involvement is present. However, the question as to whether radiation or surgery gives the best results where gland involvement is present cannot be answered by the present study. Radiation is still considered imperfect because the actual tissue dose cannot be measured and because of its untoward effect on the bladder and rectum. Best results were obtained with all types of therapy in women under the age of 50 years. This was to be expected because in these cases less dissemination was present. L. B. WINKELSTEIN.

Gynecology

Zilliacus, H., and Lehmus, H.: Early Ambulation After Laparotomy in Gynecological Cases, Acta obst. et gynec. Scandinav. **31**: 431, 1952.

The authors studied 1,511 patients who had been permitted to get out of bed shortly after laparotomy for gynecologic disease from the viewpoint of various common postoperative complications. The average hospital stay of this series was 13 days. The incidence of embolism including superficial thrombosis was 1.8 per cent; and there were 3 fatal emboli, all of which occurred without antemortem diagnosis of thrombosis. Pneumonia occurred in 1.6 per cent of the patients, but there were no deaths from this cause. Two patients died with paralytic ileus, but the basic etiology of the ileus is not mentioned. Wound disruption occurred in 1.8 per cent of the patients, and was related particularly to estimated technical skill of the surgeon in question. Of 45 cases of postoperative parametritis, 12 occurred when the operation had been performed because of chronic salpingitis, and 24 followed subtotal hysterectomy. The authors stress the obvious difficulty of relating parametritis to early ambulation. It is concluded that the various common postoperative complications have, in general, a low incidence in patients subjected to gynecologic laparotomy and subsequently ambulated early; and the social, financial, and psychological advantages of such early ambulation are stressed DOUGLAS M. HAYNES.

Donald, Ian: Aetiology and Investigation of Vaginal Discharge,, Brit. M. J. 2: 1223, 1952.

Vaginal discharge is a common complaint but should never be treated without investigation as to cause. The author advances his belief that this treatment should be administered in a special clinic wherein all diagnostic facilities are available. He reports the results in 600 patients treated in such a clinic in Chelsea Hospital for Women. Trichomonal and/or monilial infections comprised 61.3 per cent of all infections, with the peak incidence being in the 20 to 29 year age group. Patients with Trichomonas gave a history of acute onset twice as frequently as did those with monilial infections. Coitus is a frequent precipitating cause of trichomonal infection, yet 5.4 per cent of the patients

"were virgins in both the letter and the spirit." Examinations of a few husbands were negative. Trichomonal infections recurred or relapsed in 22.8 per cent of the cases, most often following menstruation, so that treatment is continued through at least three menses. Diagnosis of wet preparations in the clinic is more accurate than of cultures and dry smears.

The author advances an interesting prognostic index in which the numerical ratio of pus cells to squamous cells presages progress. For example, a P/S ratio of 0/10 is prognostically good, while a P/S ratio of 8/2 is poor, regardless of the number of organisms found. Monilial infections occurred twice as frequently as did trichomonal infections in the group using various contraceptive methods. Monilial infection is common in glycosuria, pregnancy, and gastric achlorhydria, and was concurrent with trichomonal infection in 7.7 per cent of the patients. Cervical erosions, lacerations, infections, etc., accounted for the vaginal discharge in 14.7 per cent of the total series.

An editorial in the same issue of the *British Medical Journal* agrees that a special clinic for these conditions is more efficient and more advantageous to the medical staff. It may, however, "put further out of perspective in the woman's mind what is an uncomfortable rather than a serious disorder." RANDOLPH GEPFERT.

Newborn

Bloch, Harry, Lippsett, Herbert, Redner, Bernard, and Hirschl, Daniel: Reduction of Mortality in the Premature Nursery. II. Incidence and Causes of Prematurity: Ethnic, Socioeconomic and Obstetric Factors, J. Pediat. **41:** 300, 1952.

The neonatal mortality rate of premature infants is ten times greater than that of full-term infants. Since infection is declining in importance as a cause of neonatal death in the modern premature nursery, the authors have in this paper investigated the causes of prematurity in relation to the ethnic, socioeconomic, and obstetric factors involved.

Using the clinical material available in two large obstetric services they concluded that: (1) The socioeconomic status of the pregnant mother was a major influence in determining the maturity of her newborn infant. In one service 8.6 per cent of all private patients gave birth prematurely, whereas 12 per cent of all ward patients gave birth to prematures. (2) Ethnic origin had no influence on newborn maturity. White and nonwhite mothers were similarly affected by socioeconomic factors. (3) The effect of maternal illness on prematurity was negligible, except that which influenced maternal nutrition. (4) Since 68 per cent of all premature births occurred spontaneously without any evident maternal or obstetric complication, faulty nutrition may have been an important factor in precipitating the premature labor. The occurrence of prematurity is a public health problem and related to the socioeconomic and nutritional status of the pregnant mother. HERBERT J. SIMON.

Johnson, E. K., and Mangiardi, J. L.: Diaphragmatic Hernia in the Newborn, Am. J. Dis. Child. **84:** 436, 1952.

The incidence of paraesophageal hiatus hernia is fairly low in adults while in newborn infants it is extremely rare. This case report concerns that of a 2-day-old infant with a congenital paraesophageal hiatus hernia which was successfully repaired. This is the first case of repair at such an early age and only 4 cases have been reported in older infants. The final diagnosis was verified by roentgenograms with the use of iodized oil. The operative approach was through a right rectus incision where all structures were found normal including the stomach, except that a major portion of the stomach was herniated through a hiatus 3 by 5 cm. just to the right of the esophagus. The hernia was easily reduced by traction on the stomach. Repair of the diaphragmatic hiatus was successfully carried out without undue difficulty and the infant withstood the operation satisfactorily. After a difficult start with his feedings the infant did well and

was discharged home on the thirteenth day after operation. During the next two weeks the baby did well and appeared perfectly healthy. On the thirty-first day after birth he was found dead in his crib. Autopsy revealed bilateral interstitial pneumonia. The apparent cause of death was suffocation. HARVEY B. MATTHEWS.

DeCarlo, John, Jr., Tramer, Arnold, and Startzman, Henry H., Jr.: Iodized Oil Aspiration in the Newborn, Am. J. Dis. Child. 84: 442, 1952.

This study has to do with the aspiration of iodized oil during roentgenoscopy of the esophagus in newborn babies. The oil was frequently observed in the trachea and the bronchial tree. Such a finding could be confusing in the diagnosis of abnormalities of the laryngo-esophageal region. The authors set out to investigate further these phenomena. They studied 100 healthy normal newborn babies ranging in age from 12 to 24 hours old. X-ray films of chest and abdomen further ruled out any abnormalities. These infants were then fed varying amounts of Iodochlorol (chloriodized oil) and the act of swallowing was carefully observed and the opaque agent was followed into the stomach. Spot roentgenograms were taken during this process. The infants who aspirated the iodized oil were further examined at successive 24 hour periods until aspiration ceased. Those who aspirated the iodized oil were restudied by using barium sulfate and water mixtures under the same conditions. Thirteen per cent of the infants studied aspirated the oil during the first 24 hour period. The authors conclude that the use of iodized oil for roentgenographic diagnosis of laryngeal and tracheoesophageal fistulas in early infancy is of limited value. HARVEY B. MATTHEWS.

Morton, Helen, Hennigar, G. R., and Sutton, Lee E., Jr.: Pulmonary Insufficiency in the Newborn, South. M. J. 46: 1, 1953.

Disease in childhood may manifest itself in a manner far different from that seen in the adult. Likewise pediatric pathology is not the adult picture of the disease cut down for size to fit the child. Rather it is a disease pattern peculiarly its own. This paper is devoted to the various pathologic pictures seen in association with pulmonary insufficiency in the infant. Two hundred cases of stillborn, newborn, premature, and full-term babies who died of various pulmonary complications are reported.

Primary or fetal atelectasis may be the result of immature anatomical development in the respiratory tree and in these cases no amniotic fluid or air is found in the alveoli. Secondary or resorption atelectasis is seen in somewhat older infants and these lungs have collapsed following air expansion. The most common associated findings in these cases are subarachnoid hemorrhage, tentorial tears, and subdural hemorrhage. Occasionally pulmonary hyaline membranes consisting of protein precipitate and containing little or no vernix block the air exchange in the alveolar walls. Vernix pneumonia with membrane formation, readily identified in the lung because it takes the fat stain, is not an infrequent finding in the lungs of more mature infants. Intrapartum complications which may stimulate deep fetal respirations will carry vernix into the alveoli. A bacterial pneumonia often complicates the inspiration of vernix. Mononuclear pneumonia or interstitial pneumonitis is now recognized as a cause of death in the newborn.

As the knowledge of infant pulmonary pathology progresses the term "prematurity" appearing alone on a death certificate may become a tacit admission of our own ignorance. Pulmonic insufficiency accounts for the majority of deaths of the newborn with primary atelectasis as its major cause; in the larger prematures it is hyaline membrane disease with atelectasis, while in the term infant vernix pneumonia holds first place.

WILLIAM BICKERS.

Pregnancy, Complications

Hallum, Jean L.: A Triplet Pregnancy Complicated by Thyroidectomy, Pyelitis and Anemia Followed by Menorrhagia, J. Obst. & Gynaec. Brit. Emp. 59: 527, 1952.

This case report concerns a case of triple pregnancy complicated by thyrotoxicosis, anemia, and pyelitis, followed by menometrorrhagia. Thyroidectomy, because of in-

creasing symptoms of thyrotoxicosis, was performed at the twentieth week of pregnancy. This is the generally accepted treatment and the earlier in pregnancy thyroidectomy is performed the better. Thiouracil is contraindicated during pregnancy because of its ill effects upon the fetus. In this case thyroidectomy gave relief of symptoms but the anemia persisted. At about 26 weeks of pregnancy triplets were diagnosed by x-ray. With constant and vigilant prenatal care, particularly intensive treatment of the persistent anemia, and a single attack of pyelitis, the pregnancy continued for about 33 weeks when labor began and within 9 hours triplets were born spontaneously—all boys. Their weights were 3 pounds, 2 ounces, 3 pounds, 2 pounds, respectively. The babies did well. The puerperium was normal except for the anemia. However, after the patient returned home uterine bleeding began and although vaginal examination was negative, bleeding continued intermittently. Some weeks later curettage was performed with no findings except a thick metropathic endometrium. Brisk treatment of the acute anemia, including transfusion of a pint of "packed red blood cells" and intravenous iron, was continued. Several weeks later bleeding again occurred and with severe pain and continued for 6 weeks. At this time 100 mg. of testosterone and 50 mg. progesterone were injected and the patient was referred to the endocrine clinic where under appropriate therapy menstruation has become fairly regular and without dysmenorrhea. The babies at 1 year of age weighed 19 pounds, 4 ounces, 18 pounds, 7 ounces, and 17 pounds, 15 ounces, and are in good health. The final outcome of this complicated case was most satisfactory for both mother and babies. HARVEY B. MATTHEWS.

Dabrowski, Jan: Abdominal Pregnancy, Eight Month Living Infant, Ginek. polska **23**: 81, 1952.

The rarity of such cases is mentioned, namely, only a few in the Polish literature and not over fifty cases in the world literature. This is only the fourth case of omental pregnancy. The author presents in detail the history and course of the 33-year-old gravida v, para iv, the analysis of which brings out these salient points: (1) bleeding following hot abdominal packs and the lack of signs of pregnancy in the uterus, (2) the fetal head blended with the uterus so that it was impossible to differentiate the two until the time of the operation, (3) the lack of decidual tissue to aid in diagnosis of abdominal pregnancy, (4) the lack of vaginal bleeding throughout the pregnancy, (5) a definite association between fetal movement and bowel pain, (6) the pathognomonic x-rays. Forty-four days apart they revealed the baby in transverse presentation with the fetal head on the right and above the inlet of the pelvis. The patient collapsed at the time of the second x-ray and was operated upon immediately. At the time of operation there was no connection of the fetus with the pelvic organs. The placenta was attached to the upper left wall of the abdomen and was manually removed without difficulty after delivery of a 1,500 gram living infant. The patient died shortly after the operation from hemorrhage and heart failure and the baby died 5 days later with a diagnosis of scleroderma and bilateral bronchopneumonia. The author then reviews the literature and brings out the value of dilatation and curettage and the presence of only decidua, the value of cul-de-sac puncture, bleeding, peculiar pains, and peritoneoscopy. He discusses the fate of the infant and the fact that the majority are deformed and live no longer than 10 days, and that thus the life of the mother is of prime importance in such cases. The value of x-rays, blood, and immediate operation at the time of recognition is emphasized. The old method of awaiting the death of the fetus and obliteration of the vessels has been completely abandoned. ARTHUR G. SILSKI.

Bazarewski, Stanislaw: Delivery Complicated by the Coexistence of Diaphragmatic Hernia, Ginek. polska **23**: 77, 1952.

The author describes the course of delivery in a 33-year-old multipara with a post-traumatic diaphragmatic hernia. This patient had had a previous attempted surgical repair with recurrence. X-rays revealed the stomach at the level of the third rib and

the intestines under the clavicle. Two other such cases had been diagnosed by others at section. The case described by the author is of particular interest because the patient was allowed to go into labor and at the time of the second stage she demonstrated considerable cardiac distress because the abdominal muscles exerted pressure on the intestines which in turn pushed up through the diaphragmatic hernia on the heart. Intravenous Coramine was given to the patient and the baby was delivered naturally shortly after spontaneous rupture of the membranes. The baby was healthy, mature, and weighed 3,000 grams. The author classifies diaphragmatic hernia into three groups, namely: (1) those that lead to death shortly after birth; (2) those that produce symptoms a few months after birth necessitating surgical repair; and (3) latent diaphragmatic hernias, which produce few or no symptoms and have to be diagnosed by x-ray. A brief mention is made of the surgical repair and the high rate of recurrence and mortality.

ARTHUR G. SILSKI.

Hsia, David Yi-Yung, Taylor, Robert G., and Gellis, Sydney S.: A Long-Term Follow-Up Study on Infectious Hepatitis During Pregnancy, J. Pediat. **41:** 13, 1952.

The authors reviewed the literature which supports the theory that there is a transplacental transmission of virus hepatitis. Similarly, the literature which denies the possibility of such transmission was reviewed. The evidence to support either thesis was found to be both meager and inconclusive. Accordingly, they undertook a long-term follow-up study of infants born of mothers who had definite hepatitis.

They were able to collect fourteen cases of their own. Only one infant was carried to term and, in spite of the high incidence of prematurity, all babies survived except a pair of stillborn twins. Eleven cases were followed for a period from 6 months to 16 years and the evidence derived from this follow-up suggests that there was no transplacental transmission of virus hepatitis. Since infectious hepatitis occurs only once in every 10,000 deliveries, a plea was made to other institutions to carry out their own studies and eventually pool the results. Only in this manner can the question of transplacental transmission of virus hepatitis be resolved.

HERBERT J. SIMON.

Jacobsson, Erik: Pregnancy Following Rheumatic Fever, Acta obst. et gynec. Scandinav. **31:** 471, 1953.

This is the report of a study of the occurrence of heart disease following rheumatic fever, and in connection with this an attempt was made to obtain some idea of the effect of a subsequent pregnancy on women who have had rheumatic fever in childhood. In general, it appears that a heart lesion resulting from rheumatic fever need not contraindicate carrying a patient to term; and the strain of pregnancy was not found to be likely to aggravate the existing heart lesion. Jacobsson points out that the circumstances in each individual case must be taken into consideration, and here he follows the functional classification of heart disease of the New York Heart Association as a guide to clinical evaluation. He stresses that women with functionally compensated rheumatic valvulitis can expect to pass through one or more pregnancies without suffering any noticeable ill effects on the heart.

DOUGLAS M. HAYNES.

Toxemia

Govan, A. D. T.: Hormone Studies in Toxemia of Pregnancy, Edinburgh M. J. **59:** 35, 1952.

This is a report of studies made in Glasgow by the director of research at the Maternity Hospital there "in an attempt to interpret some of the manifestations of hypertensive toxemia of pregnancy." Confirmation was obtained of the increased concentration of gonadotropins in the sera of toxemic patients. Urine from "a severely toxemic patient" was injected into immature male rats for 14 days with the production of enlargement of

the testicles of the order of three times. The tubules were greatly enlarged and active spermatogenesis was found but only a negligible increase in interstitial tissue occurred. This suggests a pituitary rather than a chorionic origin for the gonadotropin.

Adult male rats were hypophysectomized and, after 21 days, one testicle was removed and showed degeneration of the germinal epithelium. Urine "from severely toxemic patients" was injected for 14 days which restored function in the remaining testicle. Section of the pituitary areas showed no gland tissue. A similar conclusion as to pituitary origin of the gonadotropin is suggested.

In the anesthetized rabbit, posterior pituitary extract produced the same rise in blood pressure in the animal which had been treated for two days with chorionic gonadotropin as in the control without pretreatment. The same experiment was repeated using pretreatment "with alkaline extract of sheep anterior pituitary." The blood pressure rise in the pretreated animal was twice as high and twice as long as that in the control. A third experiment using as pretreatment 15 c.c. of urine "from a severely toxemic patient" reproduced the blood pressure changes of posterior lobe extract seen to follow pretreatment with sheep anterior lobe extract. It is concluded that "chorionic gonadotropin has no influence on the action of pituitrin" and "urine from toxemic patients contains a substance which resembles the alkaline extract of anterior pituitary."

"Animals" (presumably rabbits) were injected with 0.5 to 5 c.c. of Pituitrin for up to 3 weeks with the production of only occasional areas of mid-zonal necrosis in the liver. Chorionic gonadotropin was added to the Pituitrin without changing the findings. The addition of anterior pituitary gonadotropin to the Pituitrin destroyed the animals in a few hours to three days with time variations which were related to the Pituitrin dosage. "Striking changes [were found] in the livers and kidneys which closely resembled those found in human eclampsia." (These experiments have been described in detail elsewhere.) Gross albuminuria and oliguria were produced. The same results followed the addition to the Pituitrin of urine from patients with severe pre-eclampsia.

Normal pregnant patients showed a sudden drop in both systolic and diastolic pressures as a result of the administration of TEAB (tetra ethyl ammonium bromide). Of 120 toxemic patients, 102 had "a high concentration of gonadotropin in their serum" and did not react to TEAB. Four patients with essential hypertension and pregnancy did not react. The remaining 14 patients with toxemia all reacted to TEAB and all had low concentrations of gonadotropins in the serum. "Most cases of toxemia are of humoral origin and the hypertension is related to the concentration of gonadotropins in the serum." "The increased concentration [of gonadotropins] found in cases of toxemia should be regarded merely as an indication of hyperactivity of the pituitary."

Experiments designed to study nitrogen metabolism and sensitivity to insulin in the presence of pregnancy toxemia are described. The results of these lead to the conclusion that "in many cases of toxemia there is evidence of hyperactivity of the anterior pituitary associated with resistance to insulin, excessive catabolism of protein and diminished glucose tolerance."

This report should be read in the original by those who have an interest in the investigation of the pregnancy toxemias. JOHN L. MCKELVEY.

In Memoriam

Victor Bonney

VICTOR BONNEY, M.D., M.S., B.Sc., F.R.C.S., F.R.C.O.G., eminent English gynecologic surgeon, clinician, author and teacher, honorary Fellow of the American Gynecological Society, died at the Middlesex Hospital, London, on July 8, 1953, at the age of 80.